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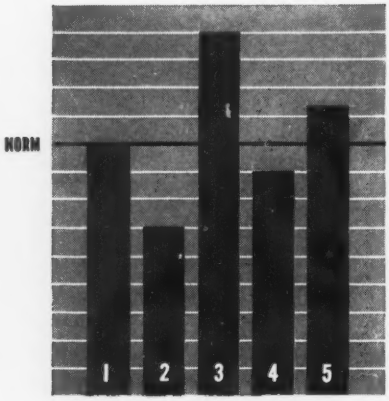

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ERRATUM—The running headline of the article by Fuller Albright in the August 1948 issue of this journal should be "Hyperparathyroidism" instead of "Hyperthyroidism."

The Journal of
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A PAGE OUT OF THE HISTORY OF HYPERPARATHYROIDISM*

FULLER ALBRIGHT, M.D.
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MEMBERS of the Association for the Study of Internal Secretions and Guests!

Two years ago, when I became president-elect of this association, I knew I would have to give this address this evening. I have worried about it ever since and am still worrying. The occasion seemed to call for something a little different than the presentation of new data. A heavy philosophical treatise, were I capable of producing such, also seemed inappropriate. I finally decided on a short historical note which is of interest not only for the facts discovered but for the means by which they were arrived at.

PATHOLOGICAL VERSUS PHYSIOLOGICAL APPROACH

What I am about to say should not be taken too literally by any pathologist or physiologist who happens to be present.

In a sense, the pathologist and physiologist approach an endocrinological problem from opposite sides. The former starts with the completed picture of the disease, learns to associate such-and-such changes in some endocrine gland with the disease, and finally comes out with a cause-and-effect relationship between the gland and the disease process in question; the latter determines what such-and-such a hormone does and deducts therefrom what the result of an under- or over-function of said hormone would be.

Received for publication June 7, 1948.

* Presidential Address delivered at the Twenty-ninth Annual Meeting of the Association for the Study of Internal Secretions on June 6, 1947, in Atlantic City, New Jersey.

The pathologist uncovers new truths by a tearing-down process; the physiologist gets at his new truths by a building-up process. The pathologist asks "*What*"; the physiologist asks "*How*" and "*Why*." The pathologist resorts to observation and to correlation; the physiologist resorts to observation and to correlation but, in addition, to the formulation of working hypotheses. The pathologist moves along step by step on firm ground; the physiologist loops along, albeit part of the time in thin air.

I shall now attempt to reduce this philosophy to a few simple diagrams. Figure 1A depicts a field of knowledge. The open circles represent unknown facts; the solid circles represent known facts. Figure 1B depicts a field of knowledge which has been exploited by a pathologist. Starting with one known fact he has, by a process of observation and correlation discovered another fact, and by the same process still a third fact, and so on, until he has elucidated quite a string of known facts. Figure 1C depicts a field of knowledge exploited by a physiologist. Here again, starting with a known fact, by a process of observation and correlation he has discovered another known fact. At this point he has made a working hypothesis (see solid circle surrounded by ring) which has led to the almost simultaneous discoveries of several more known facts, and to one more hypothesis which again has led quickly to further known facts. Figure 1D indicates a field of knowledge exploited by a less adept physiologist. By a process of observation and correlation he has discovered a new fact. But, alas! This has led to the formulation of an hypothesis which does not hold water (see solid circle surrounded by broken ring), and therefore there is no elucidation of unknown facts. So much by way of introduction!

THE AUSTRO-GERMAN PATHOLOGICAL APPROACH TO ELUCIDATION OF HYPERPARATHYROIDISM

Back in the dark ages of endocrinology, in the early 1920's, hyperparathyroidism was an unknown fact. We can think of it as an open circle waiting to be filled in. The problem was approached on the one side by the Austro-German pathological school and on the other by the American physiological school. The race ended in practically a dead heat. Thus, both lines of approach had the answer in 1926 (see Fig. 2).

The pathological approach was the older. It really won the race and should, therefore, be considered first. The scene of action, naturally enough, was the autopsy rooms of the Austro-German school of pathologists. But I am getting a little ahead of myself. Pathology is based on morphology, and I must put in a word about the discovery of these glands.

1880: Sandström discovers "Glandulae Parathyreoideae." The presence of the parathyroid glands was not known to the world until 1880,

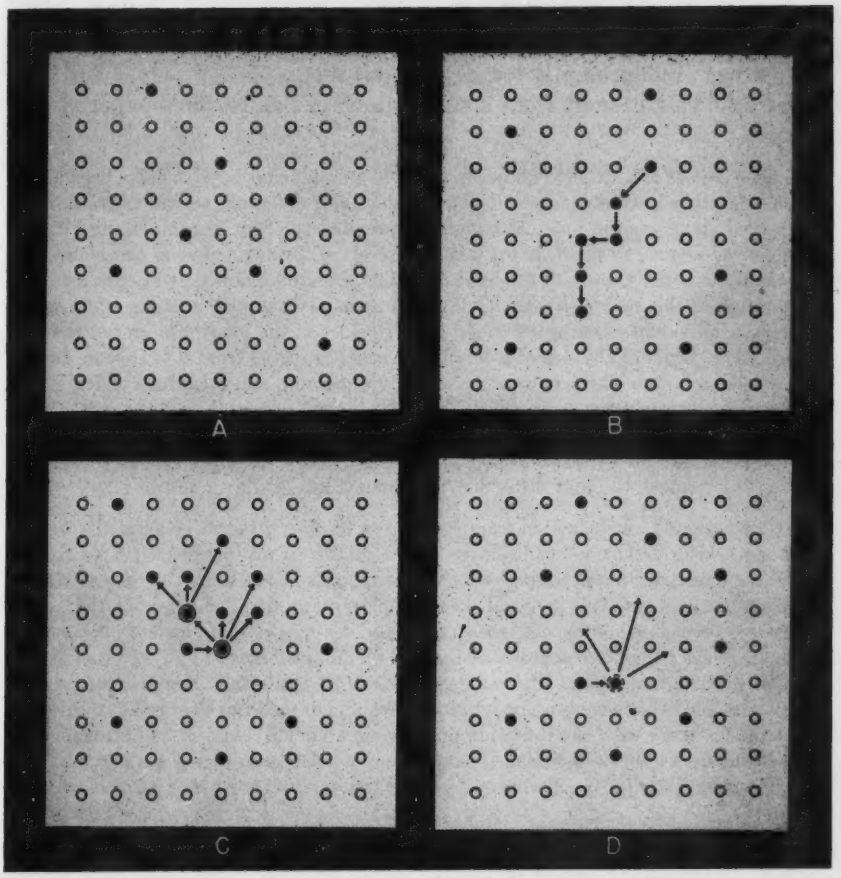


FIG. 1. Schematic diagram to illustrate how unknown facts are turned into known facts.

(A) A field of knowledge where the unknown facts (open circles) outweigh the known facts (solid circles).

(B) A field of knowledge where one known fact, by a process of observation and correlation, has led to another known fact and this, in turn, to a third, et cetera, until a whole string of known facts has been established.

(C) A field of knowledge where one known fact, by a process of observation and correlation, has led to another known fact; at this point an hypothesis was established which immediately led to several more known facts and another hypothesis, and so forth.

(D) A field of knowledge where, by a process of observation and correlation, one known fact has led to another known fact; at this point, a faulty hypothesis was arrived at which prevented the establishment of more known facts.

when their whereabouts and, for that matter, their name were disclosed by Ivar Sandström (17) from Upsala, Sweden. The world was not startled by the discovery and promptly forgot all about them.

The following excerpt from a translation* of Sandström's paper speaks for itself:

"The existence of a hitherto unknown gland in animals that have so often been a subject of anatomical examination called for a thorough approach to the region around the thyroid gland even in man. Although the probability of finding something hitherto unrecognized seemed so small that it was exclusively with the purpose of completing the investigations rather than with the hope of finding something new that I began a careful examination of this region, so much the greater was my astonishment therefore when, in the first individual examined, I found on both sides at the inferior border of the thyroid gland an organ of the size of a small pea, which, judging from its exterior, did not appear to be a lymph gland, or an accessory thyroid gland, and upon histological examination showed a rather peculiar structure."

In a letter from Sandström to his sister dated August 8, 1880, this investigator makes it clear how his discovery had fallen—shall I say—flat:

". . . I accepted an invitation from Stockholm to attend the meeting of the natural scientists (Naturforskarmotet) in order that I might do my part so that we Swedes should not succumb to our guests—which later on proved not to be the case at all. . . . One should, of course, at a personal meeting of so many men, who devote themselves to science, be inclined to expect less of a hurried reading of more or less unimportant 'products of genius' whose creators in any case would not forget to publish them, if they are of any value, than rather a friendly exchange of thoughts and a trustful communication of personal experiences and impressions. Nothing of the kind was seen . . . everyone seemed to be there with the intention of showing what 'discoveries' he had made, and at the same time give the astonished world the opportunity to have a look at the fortunate discoverer. But for the discovery itself, for the revealed truth, the interest was little or none."

The name, "glandulae parathyreoideae," was particularly well-chosen. "Para" is the Greek prefix meaning "along side of." The chief significance of the parathyroid glands for a good many years was connected with the fact that they were situated along side of the thyroid glands. People would live in regions devoid of iodine; people would get goiters; surgeons would operate on goiters; surgeons would at times remove the parathyroids along with the thyroid; some patients would get the jitters, i.e., tetany.

So much for Sandström and his glandulae parathyreoideae! I must speed on. The glands were rediscovered by Gley (2). He and others, notably Vassale and Generali (3), performed extirpation experiments in which they finally showed that it was removal of the parathyroid and not of the thyroid glands which caused the symptom-complex known as tetany. But

* This excerpt and the next were taken from a translation by Carl M. Siepel which was edited by Charlotte H. Peters and John F. Fulton and which contains biographical notes by Prof. J. August Hammar. From the Johns Hopkins Press, Baltimore, 1938.

this is another story and off on a tangent to the sequence of events which I have chosen to relate (see Fig. 2). Let us go back to the autopsy rooms of the Austro-German school of pathologists.

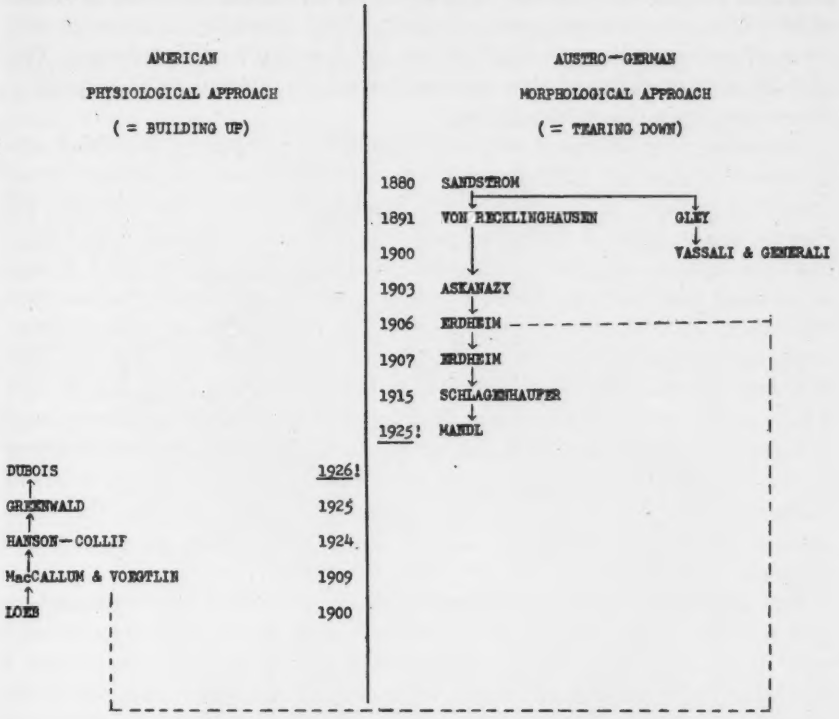


FIG. 2. American school vs. Austro-German school.

1891: Von Recklinghausen describes osteitis fibrosa cystica. In 1891, in honor of the seventy-first birthday of Rudolf Virchow, the founder of cellular pathology, his pupils published a Festschrift. One of the contributors was Professor von Recklinghausen of Strassburg, who reported on the autopsy findings, especially as related to the skeleton, in a series of 16 patients suffering from a variety of bone diseases. Of these patients, three (cases 5, 6 and 7) exhibited bone changes which were most suggestive of, if not identical with, those which are now known to be characteristic of hyperparathyroidism. And so it came to pass that the term, "osteitis fibrosa cystica of von Recklinghausen,"* became the usual appellation

* The actual diagnoses used by von Recklinghausen were: for case 5, "Verbreitete deformirende Ostitis mit Tumoren und Cysten"; for case 6, "Verbreitete deformirende Ostitis mit Tumoren"; and for case 7, "Fibröse Ostitis. Multiple Osteosarkome."

for the bone disease which so often accompanies hyperparathyroidism.

There is another bone condition which is a prominent manifestation of a very colorful syndrome and which, by the superficial examiner, is often mistaken for the bone disease of hyperparathyroidism. The other features of this bizarre syndrome—somatic and sexual precocity in females and areas of cafe-au-lait pigmentation—do not concern us this evening. The skeletal abnormalities of this syndrome are now referred to as *polyostotic fibrous dysplasia* (Lichtenstein (4)).

A number of years ago I was asked to discuss a paper by Kornblum (5) in which a case of polyostotic fibrous dysplasia was described. I re-examined patients 5, 6 and 7 of von Recklinghausen to see whether, by chance, one or more of them had polyostotic fibrous dysplasia rather than the bone disease of hyperparathyroidism. From the data at hand, it was quite clear that patients 5 and 6 did not have hyperparathyroidism but this other condition. To cite one piece of evidence, both of these patients exhibited marked protuberances in the occipital region (see Fig. 3). This is a very common finding in polyostotic fibrous dysplasia (see Fig. 4) and I have never seen it in hyperparathyroidism. Fortunately, the history and autopsy findings of case 7 are almost surely those of hyperparathyroidism or else von Recklinghausen's ghost would be in the awkward position of harboring the soul of a man who had neglected to describe the bone disease which goes under his name. But I am getting off on another tangent!

The late Herr Bleich—investigatee. With our interest in investigators and what they discovered, let us not lose sight of the investigatees and what they suffered. Let us see what manner of man was this historic case 7 and what befell him. Herr Bleich, when the curtain was raised, was a 40-year-old married mason who years before had undergone a mercury cure for syphilis. In April 1888, he fell from a three-meter high ladder onto his left side; eight days later he was admitted to the Surgical Clinic because of severe pain in his hip joint. It was not clear whether a fracture of the neck of the femur or a coxitis was present. He was treated with extension until August, when improvement was so far advanced that he began to walk with a stick. In October the patient slipped, fell against a bench, and fractured his clavicle. He was readmitted to the Surgical Clinic. There he underwent a transverse fracture of the diaphysis of the right femur while lying in bed, for a reason you would never guess—because the bedpan was clumsily maneuvered! Continued pain and unsatisfactory union made it necessary to transfer him to a nonclinical division of the City Hospital. When he was again examined in the Clinic in the course of the summer of 1889, he not only showed the most extensive bending of several long bones, but complained of excruciating pain in many bones and appeared very

emaciated. Although the fracture seemed to heal, the paitient was unable to raise the leg; marasmus increased and he died on October 4, 1889.

Von Recklinghausen made a detailed description of Herr Bleich's skeleton and emphasized three of the chief pathological characteristics of the bone disease which so often accompanies hyperparathyroidism—widespread fibrosis, cysts, and brown (or giant-cell) tumors.

One reads this accurate description and is tempted to reconstruct the

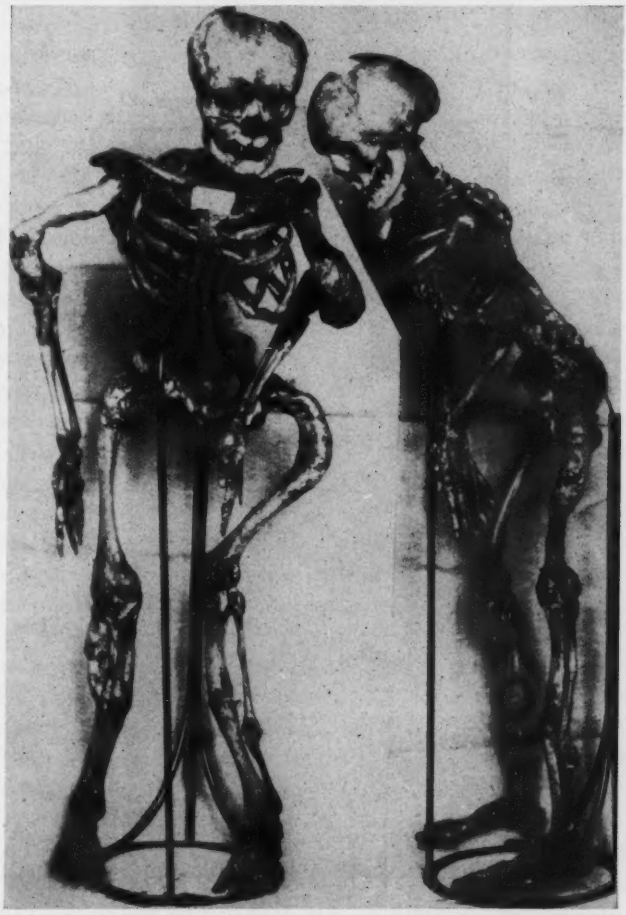


FIG. 3. Illustration from von Recklinghausen (6) usually considered to be an example of Osteitis Fibrosa Generalisata von Recklinghausen.

Because of the marked "shepherd-crook" deformities of the upper halves of the femora and because of the bulge in the occiput, (see Fig. 4) the speaker feels quite certain that this is an example of polyostotic fibrous dysplasia.

FIG. 4. Skull x-rays from three patients with Polyostotic Fibrous Dysplasia showing characteristic involvement of occipital bone. To be compared with Fig. 3.

(A) Patient A.H., M.G.H. #214900
(B) Patient N.W., M.G.H. #42709
(C) Patient A.B., M.G.H. #387989

scene. One imagines oneself at the autopsy sees the neck organs being examined; notices the little tumor in the neck; observes the great professor as he looks at this little tumor; and sympathizes with him when he does not believe the apparent impossibility—that this innocent-appearing little tumor had anything to do with the bizarre picture.

A footnote to the above scene was furnished by Jung (7) in 1933 (quoted by Thannhauser ((8)). He looked up the original autopsy report at the Pathological Institute of Strassburg and found the following comment on case 7: "Above the left thyroid gland, a lymph gland, red-brown in color is present." Reddish-brown, of course, is the characteristic color of human parathyroid tissue.

1903: Askanazy describes parathyroid tumor in a case of osteitis fibrosa cystica. The next logical step in the pathological approach was for someone to describe a case of osteitis fibrosa cystica and comment upon the parathyroid tumor; this step was made by Askanazy (9) in 1903.

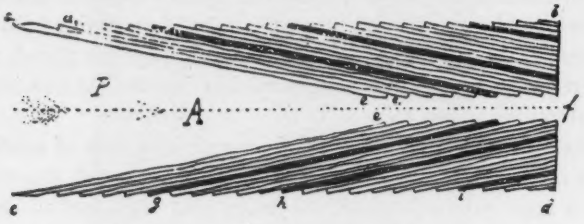
1906: Erdheim discovers relationship between glandulae parathyreoideae and calcium metabolism. Accurate observers might have gone on describing this condition for years; they might even have described the parathyroid tumors as Askanazy did; and yet they might never have suspected that the parathyroid tumors were more than incidental findings. In all probability such would have been the case, had not Erdheim (10) in 1906 noticed the crumbling teeth of his parathyroidectomized rats and focused attention on an interrelationship between the parathyroids and calcium metabolism.

Who was Erdheim? How did he happen to study the teeth of parathyroidectomized rats?

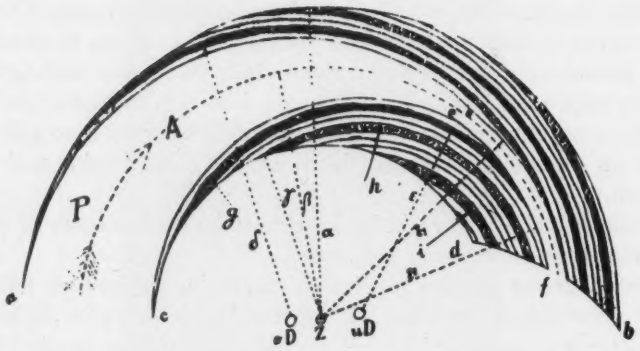
The late Professor Jacob Erdheim was an eminent Viennese pathologist at whose elbow I had the good luck to stand and gather in the pearls for one year. A very inquisitive individual, he asked, "*Was ist die Ursache?*" many times a day and found the answers surprisingly often. It is with the greatest self control that I resist spending the rest of my time on this talented investigator. I will simply state that he knew more about disease processes than any other living man. This broad statement, I am sure, will not be questioned by any of his students. So much for the man; now a word about some of his work!

In the days when they were still arguing whether it was lack of the thyroid or of the parathyroid glands that is the cause of tetany, Erdheim said to himself that one should first find an experimental animal in which the anatomy was such that the parathyroid glands could be removed without injuring the thyroid gland. It turned out that the parathyroid glands in the rat are, as a rule only two in number, are just visible to the eye, are situated on the surface of the thyroid, and can be destroyed easily

by a touch from a red-hot needle cautery. Rats were so operated on; rats developed mild tetany. The Professor sat up nights in order to record the number of seizures in twenty-four hours. Then the animals were put away in a cage. At the end of several weeks the Professor examined them. Their teeth were a little off-color. Whereas normally rats' teeth have a translucent appearance, the teeth of these animals were quite opaque. *Was ist*



Geradliniges Schema vom Wachstum des Dentins.



Natürliches Schema vom Wachstum des Dentins im Nagezahn.

FIG. 5. Schematic diagrams from Erdheim (11) to show how dentine is laid down in layers from the pulp cavities of the rat's tooth.

die Ursache? This was a difficult question to answer. Very little was known about teeth in general; less about rats' teeth. A technique had to be developed for cutting teeth into thin microscopic slices. Innumerable difficulties had to be overcome. They were. When the mist had cleared away, the facts were simple, irrefutable. The rat's incisor tooth, like that of the beaver, is constantly growing from the pulp cavity and wearing off at the gnawing end (see Fig. 5). Thus, if a tooth, for any reason, does not meet the corresponding one from the opposite jaw, so that the wearing-down

process is absent, it may grow unchecked until it enters the tissue in the neck and kills the animal, at least so the yarn goes. Between the pulp cavity, where new layers of tooth material are being put down, and its wearing-off surface there are layers of dentine in which are recorded the status of the calcium metabolism for each day during a period of several weeks. One is reminded of the Natural History Museum in New York, where one can see giant red-wood trees in cross-section. Each ring in the grain represents the growth for one year. Dry seasons and wet seasons since before the birth of Christ are represented by thin or thick rings. To return to the rat's tooth, it became clear that, from the minute the parathyroid glands were removed, the new layers of tooth contained insufficient calcium. A further experiment was performed. The parathyroid glands were removed. A period of days was allowed to elapse. Parathyroid glands from other animals were implanted. Another period of days was allowed to elapse. The animals were killed. The teeth were sectioned. Reading from the wearing-off surface inward, there was: first, normal tooth representing the layer of tooth formed before the glands were destroyed; then, tooth without calcium as was to be expected; then, a band of tooth with calcium, representing the effect of transplants. Now, after years have elapsed and the parathyroid hormone can be bought in a bottle, this same experiment has been repeated. Figure 6 shows the tooth of a rat in which the parathyroid glands were first removed and then in which, after a lapse of two weeks, parathyroid hormone was injected for a period of two weeks.

From this early experiment of Erdheim the conclusion was drawn that calcium is not deposited into growing teeth in the absence of the hormone of the parathyroid glands. This was the clue which directed the attention of all subsequent parathyroid investigators in the direction of calcium, and which was followed in two entirely different ways by the American and Viennese schools..

1906: Erdheim describes compensatory hyperplasia of parathyroids in osteomalacia. Having discovered a relationship between the parathyroid glands and calcium metabolism, Erdheim, then assistant to Professor Weichselbaum, obtained permission to examine the parathyroid glands in all cases of bone disease. In 1907 (12) he described enlargement of multiple parathyroids in patients dying of osteomalacia. In 1914 (13) he announced similar enlargement of multiple parathyroids in spontaneous rickets in rats.

From his experiments on rats, Erdheim concluded that the enlargement of the parathyroids in osteomalacia is compensatory. The two crucial rat observations were these: A) parathyroidectomy leads to *a*-calcification of the dentine of rats' teeth just as does rickets; B) all the parathyroids in spontaneous rickets in rats are enlarged. Therefore, Erdheim maintained,

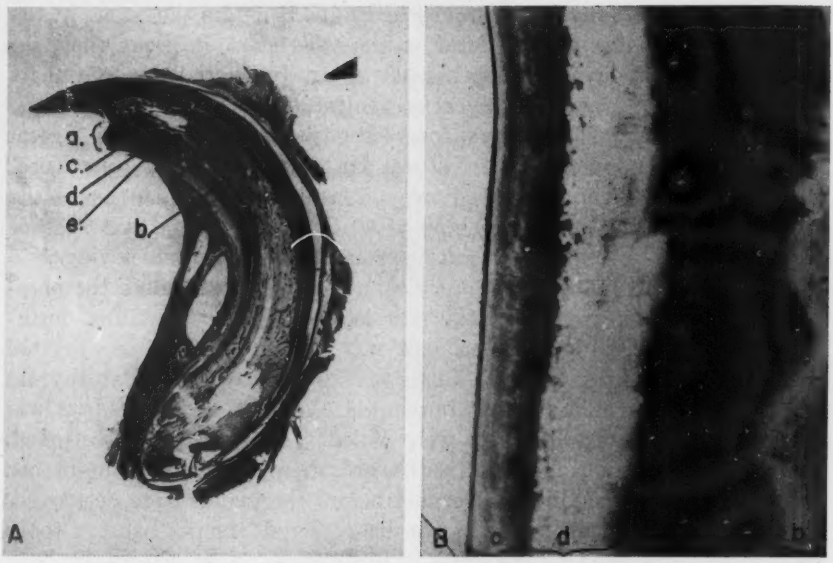


FIG. 6. Effect of parathyroidectomy and of parathyroid extract on calcification of the dentine of a rat's tooth.

The rat was parathyroidectomized and after a period of two weeks was treated for two weeks with daily injections (except on Sundays) of parathyroid extract.

(A) Sagittal section through tooth: a—dentine, b—uncalcified dentine or dentinoid, c—band of calcified dentine laid down before parathyroidectomy, d—band of uncalcified dentine laid down during the period of parathyroid hormone insufficiency, e—band of calcified dentine laid down during period of parathyroid hormone injections.

(B) Higher power of boxed-off area in A. Note two faint lines of uncalcified dentine in e-zone representing two Sundays when the rats did not receive injections. (Erdheim, J., and Albright, F.: Unpublished data.)

the changes in the teeth in rickets occur in spite of hypertrophy of the parathyroids and would be worse if hypertrophy did not occur. In short, the hypertrophy is compensatory and probably beneficial.

1915: Schlagenhaufer maintains that parathyroid tumors in osteitis fibrosa cystica are primary. The next step took almost twenty years. The delay was due to a dispute and, as in most disputes, the two sides turned out to be talking about two different things

The Viennese school continued to do autopsies and continued to describe parathyroid hypertrophy in osteomalacia; what is more, it became common knowledge in Vienna that a single parathyroid adenoma is a common finding in von Recklinghausen's disease of bone. But, because Erdheim said that the parathyroid hyperplasia is secondary in osteomal-

acia, because the possibility did not occur that what is true for osteomalacia might not be true for von Recklinghausen's disease, they continued to think of the parathyroid tumors as secondary and beneficial.

Not that there was no minority opinion! A few bold voices, notably that of Schlagenhaufer in 1915 (14), from time to time pointed out in heated debate in the famous *Gesellschaft der Aerzte* in Vienna that in von Recklinghausen's disease of bone the parathyroid enlargement involves only one gland, which would be hard to explain if the hypertrophy were secondary.

To set the record straight, it being badly garbled by many of the reviewers, I wish to say a word in defense of Professor Erdheim. He is pictured as having led the opposition to the removal of the parathyroid tumors in von Recklinghausen's disease of bone. As a matter of fact, he never expressed himself regarding this point. What he said about osteomalacia was and still is correct.

1925: Mandl removes parathyroid tumor from patient with osteitis fibrosa cystica; Albert—investigatee. But you cannot fool all of the people all of the time!

The setting remains in Vienna. The clinic is that of Professor Anton von Eiselsberg, a pupil of Billroth, the great pioneer of abdominal surgery. The leading part in the ensuing drama is played by Felix Mandl, a pupil of von Eiselsberg.

A patient enters the clinic who is destined to become famous, so let us pause briefly for patient identification. His first name was Albert; his family name has not been divulged. Albert happened to be a streetcar conductor of thirty-eight. It is not surprising that at five years he had chicken pox and at six years measles; it is little more surprising that at nineteen years he contracted syphilis. He fought for the emperor Francis Joseph in the First World War. He was sent home, from the front however, because of pulmonary tuberculosis. Such was Albert's background. In 1921 he began to complain of pains in his legs and hips and of a sense of tiredness. These pains were made worse by movement and by sneezing and coughing. He had to give up work and be pensioned. He was given various forms of treatment: mercury for his syphilis, cod liver oil for his bones, and electrical treatments for God knows what. He was given mud baths in the belief that the trouble was rheumatism or arthritis. The condition had its ups and downs but mostly its downs. In 1923 x-ray studies were made. Not only were the bones transparent, but they contained cysts. In October, 1924, Albert came to the hospital on his crutches. By that time his gait was uncertain and his back was crooked. The diagnosis of von Recklinghausen's disease was clear.

The same controversy again arose as to which is the cart and which the horse. If the adenoma of the parathyroid gland is compensatory, treat-

ment with an extract of parathyroid glands of animals should help. This was tried. It did not help.

In December, 1924, the inevitable happened. Albert stumbled and broke his leg. By this time he could not walk, stand or sit. A white sediment was noted in his urine.

Perhaps, it was thought, the extract of the animals' parathyroid glands were not potent. Another experiment is tried. There is an accident in the street; a man is brought in in a dying condition. He dies. As soon as the heart stops, Mandl removes the four parathyroids from the dead man and transplants them into Albert. Again no improvement!

Albert's situation was desperate. He was fast reaching the skeletonless, or jelly-fish stage. July 30, 1925 came. Before it had passed, Mandl (15) had taken the bull by the horns; he had operated on Albert; he had found a parathyroid tumor; he had removed this. The unbelievable happened. Within six days the white sediment, which was really calcium, had disappeared from the urine. The skeleton was no longer being dissolved and excreted in the urine. Soon the pain in the bones began to disappear. By October Albert was on crutches again. Soon x-ray examination showed the bones beginning to fill up with calcium. A patient with the heretofore fatal disease had gotten well. The riddle was solved. The story which began with rats' teeth ended with the saving of Albert's life. His name had been added along with that of Herr Bleich to the role of immortal investigatees.

AMERICAN PHYSIOLOGICAL APPROACH TO THE ELUCIDATION OF HYPERPARATHYROIDISM

In the meantime, the same answer was in the process of being arrived at across the Atlantic by men who didn't have such opportunities to see autopsies, men to whom von Recklinghausen's disease was all but unknown, let alone the fact that parathyroid adenomata were commonly associated with it. But these men had the advantage in another way; they worked in well-equipped laboratories and had adequate money for animal experiments and chemical determinations. The story is very different.

1900: Jacques Loeb finds that calcium in body fluid keeps muscles from constantly contracting. What happens if one changes the environment of the cells, i.e. changes the composition of body fluids? This is a fundamental question and was attacked by an investigator of fundamental things, Jacques Loeb (1859–1924). He was the same Loeb who, as head of the Department of Experimental Biology of the Rockefeller Institute, startled the already sufficiently excited world in 1916 with the artificial fertilization of frogs eggs. Fatherless frogs! Virgin birth in the laboratory! Science will catch up to religion yet. But the experiments which concern us here are less sacrilegious. A muscle was taken from a living frog and surrounded

with an environment of water and table salt. The muscle contracted rhythmically. Now calcium was added to the environment. The muscle stopped contracting. Loeb concluded that we owe it to the calcium in our blood that our muscles are not continuously twitching.

1909: MacCallum and Voegtlin find serum calcium level low in hypoparathyroidism. The scene changes to Baltimore where a great renaissance in American medicine was being enacted under three leading spirits, Osler, Welch and Halstead. Working with Welch in 1909 were W. J. MacCallum and Carl Voegtlin. They put two and two together and got four. The parathyroids, they reasoned, have something to do with calcium (Erdheim and rats' teeth); calcium in our blood prevents our muscles from constantly twitching (Loeb and frogs' muscles); hypoparathyroid tetany is associated with an increased excitability of the muscles; ergo there is too little calcium in the blood in hypoparathyroid tetany. They put this hypothesis to the test. Dogs lost their parathyroids. Dogs developed tetany. Dogs' blood did contain too little calcium. Dogs with tetany ceased to have it when calcium was injected into the blood. Again science had advanced. There was now a rational means of treating tetany in humans. The patient with tetany who receives an injection of calcium and derives instant relief is indebted to the experiments of Loeb on frogs' muscles, the experiments of Erdheim on rats' teeth, the experiments of MacCallum and Voegtlin (16) on dogs' parathyroids. N.B. all ye who are antivivisectionists!

Hanson (1924) and Collip (1925) independently extract active principle of parathyroid glands. The Johns Hopkins investigators had done more than point out the cause of the increased excitability of the nerves in tetany. They had furnished an accurate measuring stick for the parathyroid hormone. Something to measure is almost a *sine qua non* for the advancement of science.

Once the measuring stick for the identification of the active principle of a gland is on hand, it is time for the chemists. There were, of course, delays. Accurate methods of determining calcium in body fluids had to be developed. Soon these were ready. The time was ripe, insulin had just been isolated. The parathyroid glands of animals from slaughter houses were then subject to various processes. Brews were made. Each was injected into parathyroidless animals, and the effect on the blood calcium level noted. There was no working in the dark. Either the active principle was there or it was not. In 1924 it *was* there and, as so often is the case when the time is ripe, it was there in two different laboratories, that of Dr. A. M. Hanson (17) and that of our own Dr. J. B. Collip (18).*

1925: Collip finds high serum calcium level in experimental hyper-

* President of the Association for the Study of Internal Secretions, 1925–26.

parathyroidism. But Collip did not stop there. The inquiring mind always goes on. He studied the effect of excessive doses of parathyroid extract on dogs (19). He found many things, but the most significant for the present discussion was a serum calcium level elevated above normal (cf. low serum calcium level in hypoparathyroidism).

1925: Isadore Greenwald finds that parathyroid extract puts dogs into negative calcium balance. The next important step was made by Isadore Greenwald working alone in an experimental laboratory in the Roosevelt Hospital in New York City. We have seen that the serum calcium level is low in hypoparathyroidism (MacCallum and Voegtlin) and high in hyperparathyroidism (Collip). It had been suggested from the work of MacCallum and Voegtlin that the urinary calcium excretion is increased in hypoparathyroidisms*; *a priori* it seemed likely that the urinary calcium excretion would be decreased in hyperparathyroidism. Greenwald put the question to the test. Lo and behold! the giving of parathyroid extract in excess to a dog results in an increased excretion of calcium from the body! The high serum calcium is not the result of a low calcium excretion but the cause of a high calcium excretion.

How did matters stand at this point? Investigators on this side of the Atlantic had no inkling that such a thing as hyperparathyroidism existed but, if it did, they knew that it would be associated with a high serum calcium level and probably with decalcification of the skeleton.

That brings us to Charles Martell, investigatee.

Charles Martell—investigatee—(See Fig. 7). In 732, at the battle of Poitiers, Charles Martell rescued the Christian world from the clutches of the Saracens. But our story concerns another Charles Martell, another battle, another kind of rescue.

While Albert was fighting for Francis Joseph, his American counterpart, Charles Martell, was navigating officer for transports in the service of Uncle Sam. Our knowledge about him is less fragmentary that that dealing with Albert. We know that he was born in Somerville, Massachusetts; that he entered the Massachusetts Nautical School in 1914 to be trained for the American Merchant Marine; that he graduated in 1916 at the top of his class; that in March, 1917, he was cadet officer on S. S. *New York* when she was mined near Liverpool with Admiral Sims and staff on board only a few hours after the United States had entered the war; that the end of the war found him navigating officer on the U. S. Army Transport *Shoshone*. But a different Captain Martell came back to Somerville after the armistice. His battle was just beginning; that of his brother

* This observation by MacCallum and Voegtlin was in error due to the imperfect method of measuring calcium at that time.

Captain Judson Martell of E Company 60th Infantry, was over and the D. S. C. in his mother's possession and a grave in France tell the story.

Armistice Day, November 11, 1918, can be used as well as any other date to mark the beginning of the struggle which was to add a second Charles Martell to the ranks of the immortals, a struggle which was to

FIG. 7.

(A) Captain C. M. merchant mariner;
(B) Captain C. M., investigatee.

terminate fourteen years later on the twelve hundredth anniversary of the battle of Poitiers. This struggle was not to be against warlike Germans or ferocious Saracens but against an inward, hidden enemy—a damned elusive one to boot—which never surrendered until pickled and imprisoned in a bottle. The field of battle was not to be glamorous, but the struggle was to be carried on in one hospital ward and then another, in first this

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operating-room and then that. . . . and then this again. An unqualified victory was not in store; rather defeat in victory—or was it victory in defeat? But that is getting ahead of our story.

Captain Martell continued for a while the life of the sailor. Already at the time of the Armistice he had noted pains in his back. But one did not have to look far to find a seemingly good explanation for these—a strain while pulling on some rigging, a touch of rheumatism due to a drenching, a thousand possible explanations. But the pain persisted. Later the pain spread to his legs. In 1919 his fellow officers began to notice that he was losing in height and becoming pigeon-breasted. At about this time he noted that he passed a small amount of gravel at the end of urination. Then one day, while he was climbing a ladder, there was a slight twist, and something in his knee collapsed. For the first time the Captain was confined to bed, and, when his ship came to port a month later, he was taken to U. S. Marine Hospital No. 21 on Staten Island. X-rays were taken. Little was accomplished. The next month found the Captain on the S. S. *Swanee*. Shortly thereafter he stepped from the ships' gangway to a small launch, and his other knee gave way. One certainly gets the impression that there was something fundamentally wrong with the structure of the Captains' under-pinnings.

Hospital entry No. 2 was in the Methodist Episcopal Hospital in New York City, where an operation was performed on his knee, a patch-up job. Then followed, in rapid succession, more trips, now to the West Coast of South America, now to the Orient; there were more consultations with doctors at this and that port; more disabilities; more pains; and still gravel was noticed at the end of urination. Hospital entry No. 3 was in June 1922 at the Government Hospital, Ancon, Canal Zone, for a fractured arm. Another repair job was done, and off he went again. But not for long. He tripped over a rug on his return to New York, broke his forearm, and came under the care of a physician in New York, who diagnosed an "arthritis of the mixed perisynovial and hypertrophic type" and advised "open air life with hospital care."

It became clear after two years stay at the Marine Hospital on Staten Island that he had a disease which involved all his bones. The criteria for the diagnosis of von Recklinghausen's disease were almost unknown in this country at that time. The Captain was sailing on uncharted seas. If he was to reach port safely, the seas had first to be charted. This was no usual situation. It was a problem for investigators, and the Captain for the time being was to become the investigatee. The Captain's fifth hospital entry landed him at Bellevue Hospital in New York City. The listener knows the diagnosis and knows what should be done about it; the listener knows the chart that the Captain needs; the listener knows that such a thing as von Recklinghausen's disease exists. Let's see who took care of him at Bellevue; what sort of a person he was; how he went about this problem,

what he did. Captain Martell entered the service of Dr. Eugene F. DuBois

DuBois' background was strikingly different from that of Mandl. He came from a breed of investigators who took less interest in structure but regarded function as pre-eminent. His academic grandfather was Carl von Voit (1831–1908) of Amberg, Germany. That gentleman did not spend his nights at the microscope studying cells, learning to correlate a certain cell structure with a certain disease; but, instead, he induced Maximilian II of Bavaria to build for him a respiratory chamber, a glorified glass box in which he could enclose an experimental subject. From the nitrogen eliminated in the urine and the carbon dioxide eliminated in the expired air he calculated the amount of protein, fat, and carbohydrate being broken down in the body. He did many other things. He had brilliant students. One of the greatest was the late Professor Graham Lusk of Cornell University. The whole science of nutrition and energy-exchange in the body was attacked by the pupils of Carl von Voit. A pupil of Graham Lusk was DuBois.

When investigator DuBois met investigatee Martell, the logical results was investigation. But where to begin? The listener having had marshalled before him all the pertinent facts, doubtless is saying to himself that the answer is easy. All big advances sound simple in the telling. Remember, however, that the Albert-Mandl drama was still in the acting stage, not in the being-cast-on-the-water stage; remember that the association of a generalized bone disease with a parathyroid tumor was virtually not known this side of the Atlantic. But if DuBois and his colleagues—Roger Hannon, our own Ephraim Shorr, and W. S. McClellan—knew little about the parathyroid tumors in von Recklinghausen's disease, they did know about Collip's work; they did know a measuring stick for determining the degree of parathyroid function; and they gained a place in medical history by applying this measuring stick (20).

A sample of blood taken from the vein of Martell's arm contained more calcium than normally should be there! Here was a clue. DuBois and Co. immediately took advantage of this lead. They prepared an experiment. They measured the calcium which the Captain ingested and that which he excreted. They found that more was going out than was coming in. This paralleled the findings in Greenwald's dogs which received an overabundance of the bottled parathyroid extract of Collip. It agreed with some data which were being obtained at the Massachusetts General Hospital. The tentative diagnosis of an overproduction of parathyroid hormone (hyperparathyroidism) was made for the first time in this hemisphere, for the second time in the world.*

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* The findings on Captain Martell were presented under the title of "A Case of Hyperparathyroidism" before the thirty-ninth meeting of the Interurban Clinical Club in New York City on December 4, 1926, by Dr. Eugene DuBois.

That really ends the story. From this point on, the saga of Captain Martell does not pertain to the present discussion: how he went to Boston where Drs. Joseph C. Aub and Walter Bauer (21) found his calcium metabolism similar to that of a normal man receiving 100 units of parathyroid extract daily*; how he underwent six explorations without a parathyroid tumor being found; how he took a scientific interest in his own case and became investigator as well as investigatee; how, on the seventh parathyroid exploration Dr. Edward F. Churchill split his sternum and found the parathyroid tumor hiding behind it; how, his mission completed and an autopsy arranged for, he died shortly thereafter as the result of a combination of complications.

Thus, on the continent the disease was pulled to pieces, bit by bit without the benefit of chemical determinations: in America it was put together by a group of men, almost no one of whom had ever looked a parathyroid cell face to face in a microscope.

All of which proves that there are two ways of killing a cat (see Fig. 8).

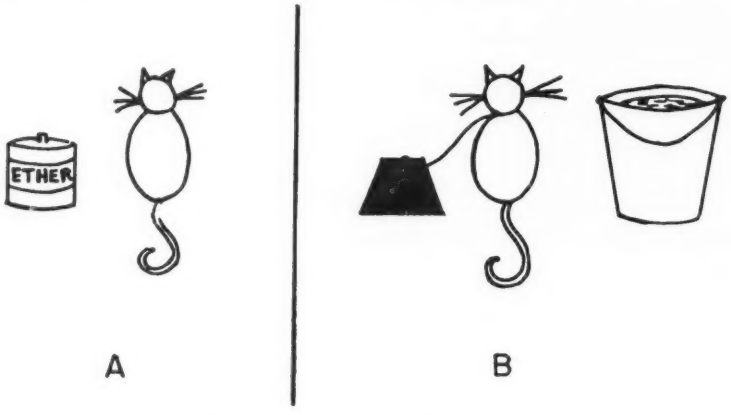

FIG. 8. Two ways of killing a cat.

At the Massachusetts General Hospital we prefer "A."

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* The Speaker has not left his name out because of modesty; he did not join Dr. Aub's group until after the diagnosis of hyperparathyroidism on Captain Martell had been established and the first operation performed.

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DEATH, PROBABLY DUE TO POTASSIUM DEFICIENCY, FOLLOWING CONTROL OF DIABETIC COMA*

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SINCE Holler's report of a patient with potassium deficiency occurring during the treatment of diabetic acidosis (1), and prior to the reports by Nicholson and Branning (2) Martin and Wertman (3, 4) and Frenkel, Groen and Willebrands (5), we have had the opportunity to observe a similar condition which terminated fatally without the benefit of specific potassium therapy. The need for more general recognition and treatment of the disturbances in mineral balance which occur in diabetic acidosis and coma have prompted us to report this patient's condition.

CASE REPORT

M. P., a 37-year-old woman, for seven years known to be a diabetic, was admitted to the hospital on January 2, 1947, in severe acidosis. For several weeks prior to admission, she had been taking daily 15 units of regular insulin and 25 units of protamine zinc insulin, but had not adhered to any particular diet. Three days before admission, she developed anorexia, nausea and vomiting; because she did not feel like eating she took no insulin. At the time she entered the hospital, she had been semicomatose for approximately twelve hours.

The patient was married and the mother of three healthy children. One year before the present illness, tuberculosis of the right lower lobe of the lung was discovered and successfully treated by phrenicotomy and pneumoperitoneum. There was no history of tuberculosis, diabetes or recurrent paralysis in other members of her family.

Physical examination revealed a thin, poorly nourished, extremely dehydrated, stuporous individual with moderately pale skin and mucous membranes. Her temperature was 99.6° F., the respirations 30 per minute, and the blood pressure 90/55 mm. of mercury. The pulse was small and regular and the rate was rapid—144 per minute. The respirations, while increased in amplitude, were not of the classical Kussmaul type. The breath smelled strongly of acetone. There was a short, healed linear scar from phrenicotomy on the right side of the neck. The breasts were small and flabby. The right diaphragm was high and immobile—confirmed by x-ray examination; fine crepitant rales could be heard in the right base and perihilar regions. The abdomen was normal except for some epigastric tenderness. Aside from the stupor, there were no positive neurologic changes. The patient was able to move herself and cooperated feebly in the examination. Rectal and pelvic examinations were deferred.

On admission, the blood glucose and nonprotein nitrogen were 345 and 33 mg. per 100

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* The biochemical determinations were made possible through a grant-in-aid from the New York Diabetes Association, as part of a study of diabetic coma.

cc., respectively, and the carbon dioxide combining power of the plasma was 9 volumes per cent.There were 4,130,000 red cells and 11,400 white cells per cu. mm. of blood; the hemoglobin was 66 per cent. Of the white cells, 64, 34 and 2 per cent were polymorphonuclear neutrophiles, lymphocytes, and large mononuclear cells, respectively.

Shortly before admission to the hospital, the patient had received 40 units of regular insulin and 25 Gm. of sugar in a large glass of orange juice. Fifty additional units were given as soon as blood was taken for laboratory studies, and an infusion of Ringer-lactate solution, containing 25 Gm. of glucose was started immediately thereafter. In addition, a proctoclysis of 4 per cent sodium bicarbonate solution was begun. Urine specimens were collected through a retention catheter.

Through gastric lavage, which the patient resisted very vigorously, 900 cc. of brownish fluid was obtained, which gave a strong reaction for occult blood. Following this her restlessness continued, did not yield to sodium luminal in a dose of 2 grains intramuscularly, and eventually necessitated physical restraint. Within six hours she had become quieter, restraints were removed, and it was noted that body musculature was somewhat flaccid. By this time, nine hours after admission, she had received approximately 4,000 cc. of Ringer-lactate solution by infusion and hypodermoclysis, to which 75 Gm. of glucose had been added; 1,000 cc. of 5 per cent glucose infusion in isotonic saline solution and 215 units of regular insulin. At this point, the acetonuria had decreased and urinary output was satisfactory; but glycosuria, probably because of the infusions, was still great. The carbon dioxide combining power of the plasma was 25 volumes per cent.

During the ensuing three hours, the patient lapsed into deep coma, despite the fact that ketonuria disappeared and glycosuria diminished. Her previously somewhat deep, although rapid respirations, were replaced by shallow, quick gasps, accomplished principally by bringing the accessory respiratory muscles of the neck into play. On examination of the lungs, there was no sign of edema or of mechanical obstruction; the left diaphragm moved but slightly. There was no evidence of circulatory collapse; the pulse was regular, 120 per minute, and of better quality than on admission. The blood pressure had risen to 110/65. Oxygen by closed mask, and caffeine and coramine intramuscularly were given without material improvement in her condition. For the following nine hours, *i.e.*, between the twelfth and twenty-first hours after admission, there was little change in her status. The urine remained acetone-free, and the sugar small in amount. An electrocardiogram taken during this time showed a sinus rate of 94 per minute, a P-R interval of 0.18 sec., slurring of the QRS complexes, flattening of the T-waves, and sagging of the S-T segments in all three limb leads.

At the twenty-first hour after admission, she was placed in a mechanical respirator which resulted in some improvement in her condition. It was at this time that the possibility of a potassium deficiency was first considered as a cause for her condition. Chemical analysis of the blood revealed values in mg. per 100 cc., for glucose, 400; nonprotein nitrogen, 38; creatinine, 1.5; sodium, 330; and potassium 4. The carbon dioxide combining power was 43 volumes per cent. An unsuccessful attempt was made to give potassium by gastric tube, while an infusion of 2 per cent potassium chloride could be prepared. Unfortunately the patient expired twenty-six and one-half hours after admission and before any potassium was administered.

DISCUSSION

1. **Diagnosis.** The problem in differential diagnosis presented by this patient was made materially easier by virtue of the chemical examination of the blood made shortly before death. The normal values for nonprotein

nitrogen and creatinine precluded coma on a uremic basis. At no time did hypoglycemia exist; on the contrary, hyperglycemia and glycosuria were present. The carbon dioxide combining power of 43 volumes per cent was incompatible with clinical acidosis. The only marked deviation from normal in this final specimen of blood was the potassium value of 4 mg. per 100 cc. Pulmonary edema was never present in this patient, nor was there ever any evidence of obstruction of the respiratory passages. The circulatory status improved soon after therapy was started and remained good until one hour prior to death, when the temporal pulse became weak and thready. There was no evidence of shock or cardiac failure until shortly before death.

Since autopsy was not done, it cannot be stated with any certainty what influence the tuberculosis had on the terminal illness, nor can the extent of the tuberculosis be defined. However, x-ray examination of the chest showed no cavitation; there was no significant adenopathy; renal function was not impaired, and there were no neurologic abnormalities suggestive of tuberculosis of the nervous system. It can only be said that there was no obvious evidence of extra-pulmonary tuberculosis, and the pulmonary lesion was apparently controlled.

In this case, therefore, other conditions have been eliminated by a process of exclusion, and positive evidence for a potassium deficiency has been obtained in the clinical findings and laboratory data.

Should it be difficult for the clinician to obtain repeated analyses of the blood, then a hypopotassemia should be suspected when a transient or partial relief in the patient's state of consciousness is followed by a relapse into stupor, despite a decrease or disappearance of the ketosis. When such a relapse is associated with a diminution rather than an increase in muscular tonus, and when shallow rapid respirations supervene, in which breathing is mainly due to the action of the accessory muscles of respiration, then the likelihood of potassium deficiency is even greater. In our experience (unpublished data), this clinical picture justifies the use of moderate amounts of potassium parenterally, even if complete laboratory data are not available.

2. **Potassium in relation to muscular phenomena.** Holler (1) cited the work of numerous investigators to show the relationship of a decrease in serum potassium to muscular paralysis. He also listed the conditions which favor the appearance of such a deficiency. It has been shown that the serum potassium is low during attacks of familial periodic paralysis (6, 7) and that such attacks respond to the administration of potassium salts. In patients with this familial disease it has been possible to precipitate attacks by procedures which tend to lower the potassium of the blood serum, such as forced carbohydrate feeding (7) or insulin administration (8). Moreover, Brown, Currans and Marchand (9) have reported three cases of

muscular paralysis occurring in the course of chronic nephritis, in two of which the serum potassium was initially low, and in each of which there was a response to administered potassium. The flaccidity of musculature, even to the point of paresis, is a constant feature of serum and tissue potassium deficiency.

3. **The variations in serum potassium, carbohydrate and insulin.** Insulin was not long available when it was shown that a marked decrease in serum potassium followed its administration to dogs and human beings (10, 11, 12, 13). Harrop and Benedict (11, 12) showed that insulin produced a marked decrease of serum potassium and phosphate, coincident with a decrease in blood sugar in normal individuals, in diabetes with and without coma, and in fasting dogs and rabbits. The depression of serum potassium under all the circumstances cited persisted as long as the insulin was active. It was further demonstrated that the deposition of glycogen in the liver under the influence of insulin was accompanied by a concomitant storage of potassium (14). It is believed a retention and storage of nitrogen may have a similar effect (15, 16).

4. **The behavior of potassium in diabetes.** Atchley *et al.* (17) studied 2 diabetics during periods of withdrawal of insulin and following resumption, the patients being maintained on diabetes diets throughout the experiment. In both patients, insulin withdrawal produced a sharp rise in urinary excretion of potassium, followed by retention of potassium on resumption of insulin. The patient developing ketosis showed the greater loss of potassium.

Stewart and Rourke (18) showed that in fasting, nondiabetic patients given large amounts of infusions there is an excessive loss of potassium in the urine—greater in those given isotonic saline than in those given 5 per cent glucose solution.

In the experimental production of diuresis and dehydration in dogs with good renal function Winkler and his associates (19, 20) demonstrated that the transfer of potassium from the intact cells and its excretion in the urine is a physiological response of the organism to severe dehydration.

As a part of the depletion of base during diabetic acidosis, Danowski and others (21) found that the cells had lost appreciable amounts of phosphate and potassium. High values for serum potassium in untreated diabetic coma were ascribed in part by Martin and Wertman (3) to hemoconcentration; our own experience (unpublished data) indicates that they can also be caused by disturbances in renal function in association with azotemia.

The case here reported supports the general contention that serum potassium decreases as the acidotic state improves under therapy with insulin alone or with insulin and carbohydrate (2, 3, 4, 5).

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5. **The probable role of potassium in the therapy of diabetic acidosis.** Holler (1) successfully treated his case of diabetic acidosis with 1.5 Gm. of potassium chloride as a 2 per cent solution given slowly intravenously over a period of thirty-five minutes. The respiratory paralysis was dramatically improved but soon recurred, and a subcutaneous infusion of 200 cc. of 2 per cent potassium chloride mixed with an equal amount of isotonic saline was administered. Two grams of potassium citrate were then given orally and then 1 gram hourly for two doses, with complete and permanent remission of symptoms.

Obviously, a more desirable form of therapy would have as its objective the replacement of potassium before the deficiency reaches the point of endangering the patient's life. Such a program might need to include the early use of much larger quantities of potassium than have formerly been employed.

The studies of Darrow (15) and his associates on electrolyte balance have clarified greatly the role of potassium in body-fluid physiology. These workers revolutionized the treatment of the severe dehydration of the diarrheas of infants and also demonstrated the relative safety with which large amounts of potassium can be administered parenterally in the presence of a potassium deficiency. Darrow and Yannet (22, 23) showed that from one-third to one-half of the extracellular electrolyte must be removed in order to produce the clinical picture of dehydration. This amount of electrolyte is contained in 80 to 100 cc. of physiologic saline per kilogram of body weight. The solution that Darrow (24) chose for parenteral therapy in diarrhea of infants is made by adding 40 cc. of molar sodium lactate, 2 Gm. of potassium chloride and 3 Gm. of sodium chloride to 710 cc. of water. He used 80 cc. of this solution (3.1 mM.) per kilogram body weight per 24 hours, given intravenously or subcutaneously over a period of from four to twelve hours. Heart block is produced when the extracellular concentration of potassium reaches 10 to 12 mM. per liter. Darrow says "One can predict with reasonable certainty the safe dose of potassium for intravenous or subcutaneous use. If the concentration of serum potassium is 5 mM. per liter, a rise of 4.5 mM. will not produce heart block. Assuming equal distr bution throughout body water, 3.1 mM. of potassium per kilogram of body weight will produce a rise of 4.5 mM." Darrow (24) emphasizes the necessity for treating shock if it is present, since a high concentration of serum potassium may be present in shock.

Govan and Darrow (25) in treating 50 infants with diarrhea encountered only 1 case of potassium intoxication. This occurred in an infant who had had previous potassium therapy, and in whom a potassium deficiency probably did not exist. This patient developed heart block, which disappeared during the injection of 15 cc. of 10 per cent calcium gluconate and

150 cc. of 17 per cent glucose. Five patients developed erythema on the second or third day of therapy, with subsequent roughening and desquamation of the skin. The authors emphasize the importance of intact renal function if potassium therapy is to be employed.

There is little doubt that the work of Darrow and his associates can be applied with advantage to the treatment of diabetic acidosis. The patient with severe acidosis who presents himself for treatment after several days of nausea, anorexia and vomiting has already lost considerable potassium. The large quantities of fluids and insulin which must be given can seriously aggravate this deficit, unless provision is made for adequate replacement. It is in this group of cases that the solution employed by Darrow (24), or a modification of it, should find its greatest usefulness. The milder cases of diabetic acidosis do not require vigorous potassium therapy. However, more precise data as to the excretion and serum levels of potassium during all stages of diabetic acidosis are needed before any rational therapy can be formulated. Sporadic attempts have already been made to make such determinations and some results of such treatment have been reported (2, 3, 4, 26). As yet unpublished studies, in which two-hourly determinations of serum electrolytes have been made in connection with the administration of potassium in diabetic acidosis, indicate the necessity for correlating the function of the kidney, the dose of insulin, and the amount of glucose administered. Certainly a great deal of harm can be done by the indiscriminate employment of "gunshot mixtures" of electrolytes without due regard for the needs in each individual case.

SUMMARY

1. A 37-year-old woman with diabetes of seven years' duration developed a low concentration of serum potassium (1 milliequivalent per liter) while under treatment for diabetic ketosis, and apparently died as a result of a potassium deficiency.

2. Several phases of potassium metabolism have been discussed in relation to the management of diabetic acidosis. Factors which might combine to produce a diminished supply of potassium in diabetic ketosis include: a) diuresis and dehydration with a consequent drain upon the intracellular supplies of water and potassium; b) the necessity for drawing upon the body stores of fixed alkali to excrete the large quantities of organic acids present; c) a decrease in blood and tissue concentrations of potassium as a result of the administration of fluids not containing this element; d) the action of insulin; and e) the administration and assimilation of carbohydrate.

Factors which may cause a rise in tissue and serum potassium during diabetic acidosis include a) hemoconcentration and b) renal failure.

3. Clinical manifestations due to a lack of potassium are rarely, if ever, observed in the patient with untreated diabetic coma. They may appear during treatment, particularly when a selective replacement of electrolytes is not achieved.

4. It is recommended that values for serum potassium be determined in every case of diabetic coma before and at least once during treatment, and that potassium supplements be given on indication at the proper time during therapy.

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STUDIES ON THE NONSPECIFIC CHOLINESTERASE IN THE SERUM OF THE HUMAN FEMALE*

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THE interrelationship between enzymes and hormones has been a subject of much speculation. Very little information is available regarding the mechanism by which these two classes of important biological substances interact. That these organic components do influence the activity of each other has been demonstrated amply by a number of investigations conducted, for the most part, in experimental animals.

Birkhäuser and Zeller (1) demonstrated a sex difference in the nonspecific cholinesterase activity of the liver in rats. They found the values for these nonspecific esterases were from five to eight times greater in mature female animals than in males. Beveridge and Lucas (2) found a similar but less distinct sex difference. In their studies, the values for the enzyme level of the serum in female rats were three to five times greater than those encountered in males.

More recently Sawyer and Everett (3) in a much more extensive study found that in rats, following ovariectomy, there was a rapid decline of nonspecific cholinesterase in the blood serum of mature females. Castration of males, however, resulted in a gradual and moderate rise in the titer of this enzyme. Furthermore, they demonstrated that the administration of estrogens to castrate animals caused a definite rise in the serum content, of the nonspecific cholinesterase, followed by a decline when the estrogens were withdrawn. In pregnant animals, these workers observed a progressive rise in the enzyme titer in the blood serum until shortly before parturition, when the values again declined. The results of the foregoing experiments in rats demonstrate quite clearly that there is a relationship between the levels of nonspecific cholinesterase and estrogen in the blood serum.

Data of a similar nature pertaining to human subjects are very meager. Hall and Lucas (4) studied the cholinesterase activity in a series of patients in an attempt to observe the effects of diet, age, and sex on the serum con-

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tent of the enzyme in normal individuals. They were unable to demonstrate any sex differences. In a series of nine pregnant women they were unable to show any change in serum enzyme values at various stages of gestation.

Wynne (5) demonstrated that cholinesterase in the serum of human beings is largely nonspecific in activity and Langemann (6) has shown that the human ovary contains only nonspecific cholinesterase.

In view of the interesting results obtained in the rat and the lack of a correspondingly large series of observations in the human, additional work was desirable. The following experiments were designed to study the serum levels of nonspecific cholinesterase in normal women, in women with common gynecologic diseases, as well as during pregnancy and parturition.

METHODS

In view of its simplicity and applicability for large-scale clinical studies the direct titration method (4, 7, 8, 9, 10) with slight modification has been employed.

Five cubic centimeters of venous blood was obtained from the patient and allowed to clot in a dry centrifuge tube. After clotting, the blood was centrifuged and the clear supernatant serum decanted into a clear dry test tube. One cubic centimeter of clear serum was added to a large test tube containing 10 cubic centimeters of distilled water. After addition of the clear serum the pH was adjusted to 8 by the addition of 0.01 normal sodium hydroxide, using 0.4 per cent cresol red as an indicator. The color was compared to that of a similar test tube containing indicator and phosphate buffer at pH 8. The tubes were rigidly suspended in a clear glass-walled constant-temperature bath maintained at 37.5° ±0.5° C. Twenty-five milligrams of acetylcholine chloride was added as the substrate. The time of the addition of the substrate was carefully noted and the liberated acetic acid was titrated for a period of twenty minutes. The total amount of 0.01 normal sodium hydroxide in cubic centimeters used in the titration was taken to denote the units of nonspecific cholinesterase of the serum specimen. One cubic centimeter of 0.01 normal sodium hydroxide was designated as one unit. At the start of the investigations all specimens were determined in duplicate. However, the values obtained checked so closely that this practice was later discontinued.

In a few cases mecholyl was substituted for the acetylcholine in an attempt to measure the specific cholinesterase but these values were so small after a twenty-minute period that no detectable color change could be observed. For this reason this procedure was discontinued.

Most of the determinations were made promptly after the blood specimens were obtained. In a few instances immediate determinations were

not possible and the blood was kept in the refrigerator. This procedure does not affect the activity of enzyme appreciably (11). However, none of the specimens of the present study was allowed to stand more than twenty-four hours.

RESULTS

A total of 304 determinations were made on several groups of women. The first group comprised 98 normal nonpregnant women ranging between 18 and 43 years of age. The second group consisted of 108 pregnant women ranging between 20 and 38 years of age at various stages of gestation, exhibiting no abnormal obstetrical complications. The third group was made up of 35 women in labor. The fourth group is a miscellaneous one consisting of 63 women with a variety of abnormal conditions.

Normal women. Ninety-eight clinically normal women were studied. One or more determinations were made on each individual. It was found that while there was great individual variation, the values for any one woman remained relatively constant.

The level of nonspecific cholinesterase during the various phases of the normal menstrual cycle was studied in three women. Determinations were made at three-day intervals during three consecutive cycles in each individual. A definite depression in the level of the enzyme of 1.4–2.1 cc. of 0.01 normal sodium hydroxide necessary for titration, occurred shortly before the onset of the menstrual flow. This constituted a decrease in enzyme level of approximately 15 to 20 per cent. The level of nonspecific cholinesterase in the serum remained constant throughout the remainder of all the cycles.

Pregnant women. In the group of pregnant women the same individual variations occurred as were observed in women who were not pregnant. However, individual determinations on any one patient remained relatively constant throughout pregnancy. The stage of gestation did not influence the serum level of nonspecific cholinesterase (Fig. 1).

In a comparison of the two groups, pregnant and nonpregnant, it was found that the average values in the former were somewhat lower than the values obtained in the latter. The average value in the pregnant patients was 5.96 cc. and in the nonpregnant women 6.79 cc. When these values were statistically analyzed it was found that the difference, 0.83 cc., was significant and that it would not occur once in ten thousand times unless it had a basis in fact.[1]

The levels of the enzyme in the serum during labor were studied in 35

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[1] We wish to thank Dr. Leonard G. Savage of the Department of Mathematics for these statistical analyses.

women. In 23 cases one or more determinations were made from one to sixteen days prior to the onset of labor and continued throughout their labors (Table 1). Of these, 13 showed a slight depression during active

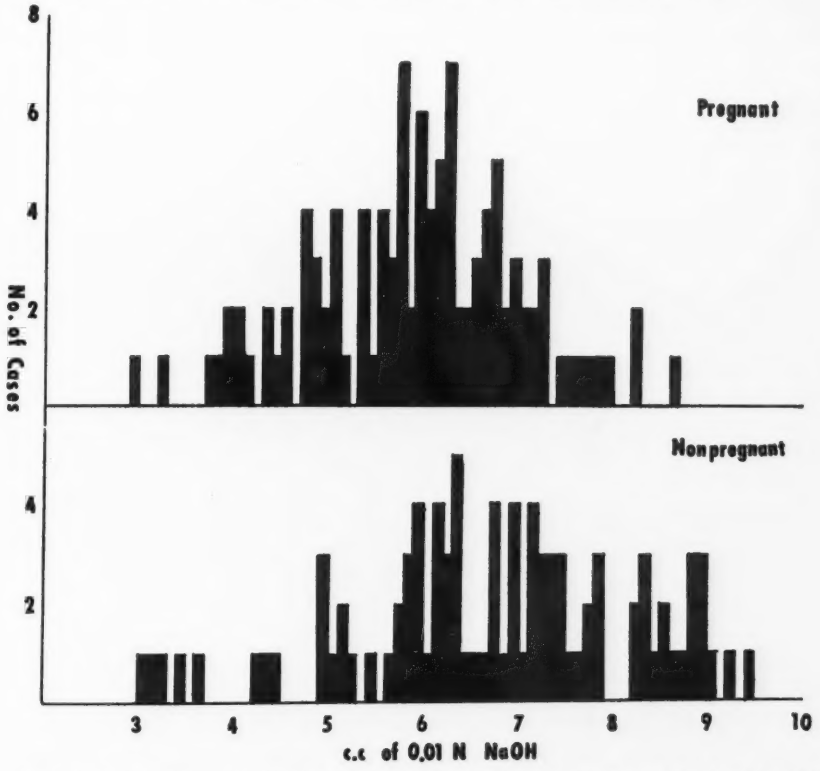

FIG. 1. Graph demonstrating the range of values for cholinesterase obtained in 108 pregnant and 98 nonpregnant women. Note that while both groups exhibit the same range of variation, the mean for the nonpregnant group is slightly higher.

labor, while 6 showed no appreciable change. The remaining 4 showed a slight elevation during active labor. In three patients who were delivered by cesarean section prior to the onset of labor, no changes in the level of nonspecific esterases were observed prior to, during and after the delivery of the baby. Thus, no specific pattern could be established during the first and second stages of labor, ending with the delivery of the child.

The placental stage, usually designated as the third stage of labor, did show a small but characteristic drop in the titer of serum cholinesterase. This depression lasted for twenty-four to forty-eight hours, following which there was a gradual rise to the normal level for the patient under

observation. The cause for the drop at this time in the level of this enzyme in serum is not known. In view of other suggestive findings we have theorized that it is associated with vascular changes inherent in the placental stage.

Included in the group of women in whom studies of the level of the enzyme in serum were made during labor, were two individuals who developed premature detachment of the placenta-abruptio placentae. This in-

TABLE 1. NONSPECIFIC CHOLINESTERASE LEVELS IN SERUM DURING PREGNANCY, PARTURITION AND THE POSTPARTUM PERIOD

Patient Number	Antepartum cc. 0.01 N NaOH	Intrapartum cc. 0.01 N NaOH	Postpartum cc. 0.01 N NaOH
1	6.7	5.8	7.1
2	5.4	5.2	5.2
3	5.1	4.3	5.6
4	5.9	5.4	5.4
5	5.7	5.3	5.6
6	5.5	4.9	4.6
7	5.9	4.2	4.4
8	6.8	6.2	5.9
9	6.0	5.8	7.1
10	5.8	5.5	6.2
11	7.9	6.4	8.1
12	6.2	6.0	6.0
13	6.8	4.7	6.6
14	6.5	6.9	6.1
15	5.9	6.3	5.8
16	6.0	7.0	5.3
17	5.8	6.2	5.9
18	6.0	6.0	7.1
19	4.0	4.0	4.8
20	5.3	5.3	5.6
21	5.2	5.2	7.0
22	5.6	5.6	6.0
23	6.2	6.2	6.0

teresting complication is related to the toxemias of pregnancy and is most often associated with vascular-renal and hypertensive disease of the mother. In contrast to the results in normal women, very low values were obtained during the management of this complication. The levels in serum did not reach normal until two weeks postpartum (Fig. 2).

These observations were so striking that several experiments were carried out to account for this unusual depression of the nonspecific cholinesterase in serum abruptio placentae. Great blood loss, often exsanguinating

in character, is associated with premature detachment of the placenta. The following studies were made in order to evaluate the effect of such blood loss and blood replacement by transfusion on the level of cholinesterase. Four women who had experienced severe blood loss in their labors and were transfused several times were followed carefully by frequent examinations, but the titers of the enzyme in serum were within normal limits.

The effect of anemia on the nonspecific esterases was determined in ten women in whom the hemoglobin was less than nine grams. No abnormally low values were encountered.

That the transfusion of citrated blood does not alter the level of nonspecific cholinesterase in the serum can be seen from the following obser-

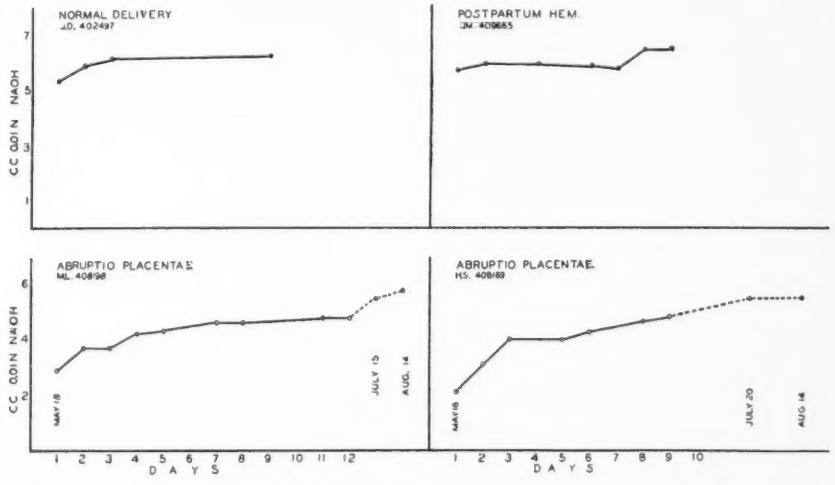

FIG. 2. Graphs demonstrating changes in titers of cholinesterase in serum during the stage of placental separation in a normal delivery (1 case), postpartum hemorrhage (1 case) and abruptio placentae (2 cases). Note the extremely low values found in abruptio placentae as contrasted with normal delivery and postpartum hemorrhage.

vations. Serial determinations over a period of three days were made on five women following transfusions of citrated blood. No change in the levels of the nonspecific esterases were noted in any of these women.

Anemia, sudden and severe blood loss and the transfusion of citrated blood do not affect the enzyme titer. Some other factor must account for the disturbed enzyme pattern which develops in patients with abruptio placentae.

Miscellaneous conditions. Enzyme levels in 63 patients with a variety of gynecologic complications were within normal limits with two excep-

tions. In three patients who had carcinoma of the cervix abnormally low values were obtained. In two patients in the menopausal group abnormally high titers were found. Further studies should be carried out to determine whether or not these findings are significant.

SUMMARY AND CONCLUSIONS

The direct titration method with slight modifications was used to determine the titer of nonspecific cholinesterase in serum in 98 normal women, 108 pregnant women, 35 women in labor and 63 women with various pathologic conditions.

In view of the experimental studies reported on the rat, our studies on the human are somewhat surprising. In our series of pregnant women the nonspecific cholinesterase of the serum remained relatively constant within wide individual variations throughout gestation. This is contrary to the progressively increasing values during gestation in the rat. Furthermore, our studies suggest that the values for nonpregnant individuals are slightly higher than those encountered during gestation. This, too, is contrary to studies on experimental animals in whom it has been demonstrated that estrogens raise nonspecific cholinesterase levels. One would expect that if the titer of cholinesterase was increased by estrogen in the human, higher values would be present in pregnant than in nonpregnant individuals. Our evidence would indicate that in the human, estrogens exert no appreciable effect on the nonspecific esterases.

The level of the nonspecific esterases in serum is not altered during the normal ovarian cycle until the onset of menstrual bleeding, at which time a moderate drop in the titer occurs. This finding, coupled with the drop in the level during the placental stage of labor and the marked depression which occurs in abruptio placentae would indicate that changes other than estrogen metabolism affect the level of cholinesterase in serum in the human female.

In a variety of pathologic conditions studied, abnormal values were found in the serum of three patients with carcinoma of the cervix and two patients in the menopause. These are too few observations to be significant, and the subject merits further study.

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THE ELECTROENCEPHALOGRAM IN HYPOPARATHYROIDISM WITH TETANY AND EPILEPSY

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PARATHYROID insufficiency, whether idiopathic or postoperative, may be accompanied by epilepsy and occasionally by psychosis in addition to the usual signs and symptoms of tetany. The study of the electroencephalogram in patients having this glandular deficiency is, therefore, of the utmost importance. Little has been written on this topic. Only one paper is known to us, namely, that by Odoriz *et al.* (1). There are a few publications, however, which contain reports of isolated clinical cases, with references to electroencephalography (Kowallis (2); Sutphin *et al.* (3); Taubenhaus and Engle (4)).

CLINICAL MATERIAL

There were 14 patients, 13 females and 1 male, in whom the diagnosis of parathyroid deficiency had been made on the basis of a definite history of tetany, signs of peripheral neuromuscular hyperexcitability and a subnormal level of plasma calcium. Their ages ranged between 21 and 43 years. In 3 cases the signs and symptoms appeared spontaneously but in 11 cases they developed following thyroidectomy for goiter. In these patients the duration of the condition varied from ten days to fourteen years. The controls were 4 normal female students whose ages varied from 17 to 31 years.

PROCEDURE

The day the electroencephalogram was recorded, blood samples were drawn from the fasting patients and Dr. Federico Vilallonga carried out the following determinations: total calcium (Marenzi and Gerschman's method (5)); inorganic phosphorous (Fiske and Subbarow's method (6)); and total protein, using Moore and Van Slyke's densimeter. Ionic calcium was calculated from the total calcium and total protein values by means of McLean and Hastings' nomogram.

Patients who were receiving calciferol (crystalline vitamin D_2) stopped this medication at least two weeks before the electroencephalogram was taken; but in order to avoid an attack of tetany, the administration of calcium salts was not stopped until twenty-four hours before the recording.

The electroencephalogram was then recorded with the patient lying on his back. Records were obtained a) during an initial rest period, b) during

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a period of hyperventilation at a fast rate for a maximum of one and one-half minutes,[1] and c) during the subsequent rest period. Following this, the patient was given 1 Gm. of "Calcium Sandoz" intravenously. After a five-minute rest, the electroencephalogram was repeated in the manner just outlined, namely, before, during and after hyperventilation. The experiments on the controls ended here but the experiments on the patients with parathyroid insufficiency continued. These patients received daily oral or intramuscular doses of 10 to 15 mg. of calciferol (400,000 to 600,000 I.U.) and 15 Gm. of calcium lactate. This treatment was followed with weekly determinations of plasma calcium. These usually showed normal values within twenty to sixty days. Return to normal plasma calcium levels was usually associated with the disappearance of the clinical symptoms of parathyroid deficiency. The investigations were then repeated. Occasionally the treatment resulted in hypercalcemia and we quickly took advantage of this opportunity for further study. After obtaining electroencephalograms in treated patients, calciferol was discontinued in four of them and tetany recurred after varying intervals. A new study was then carried out.

In all, we performed 40 electroencephalograms on the 14 patients under investigation. In 6, the electroencephalogram was recorded only during hypocalcemia; in 5, during both hypocalcemia and normocalcemia; and in 3, during hypocalcemia, normocalcemia and hypercalcemia.

A Grass three-channel inkwriting oscillograph with a paper speed of 25 millimeters per second was used for tracings. The amplification was such that 50 microvolts caused a 7 millimeter deflection on either side of the base line. Push-pull amplifiers were always used. Electrodes were placed on either side of the head on Gibbs' lines B and C. Both ears were interconnected, grounded and used as reference points on monopolar recording; bipolar records were also obtained occasionally.

CASE REPORTS

We have selected 8 cases for description because of their particular clinical or electroencephalographic interest. The values for calcium, inorganic phosphorus and protein are given in terms of 100 milliliters of plasma.

Case 1, M. Z., female, aged 38 years. Her father died of general paresis. During pregnancy, at the age of 22, she began to feel pains in the extremities. Later she developed rotary vertigo, attacks of tetany, and of epilepsy consisting of sudden loss of consciousness, tonic convulsions, tongue biting and frothing of the mouth. These attacks lasted about half an hour and were followed by amnesia. At the age of 25 she developed posterior and

[1] Hyperventilation could not be carried out for more than one and one-half minutes, sometimes less, because it tended to produce attacks of tetany.

anterior cortical cataracts for which she was successfully operated upon ten years later. She derived no benefit from a parathyroid graft done when she was 30 years of age. She had several manic episodes at the age of 36.

On May 22, 1944, the laboratory reported the total calcium in plasma as 6.4 mg., ionized calcium 2.7 mg., inorganic phosphorus 6.68 mg. and total protein 6.9 Gm. *EEG I:* throughout the cortex, the electroencephalogram showed predominantly a fast rhythm of 26 to 30 c/s. In the midparietal area there were single spikes and an isolated parieto-occipital discharge of 70 microvolts, 5 c/s frequency. During hyperventilation there were slow waves (6 c/s) in series of 3 to 4 waves, particularly in the frontoparietal leads. These waves disappeared after hyperventilation ceased.

On June 6, 1944, the total calcium in plasma was 10 mg.; ionized calcium 4.4 mg.; inorganic phosphorus 4.86 mg. and total protein 7.07 Gm. *EEG II:* the electroencephalogram was similar to the first one. During hyperventilation the 5 to 7 c/s slow waves recurred.

Case 2, A. C., male, aged 21 years. This patient, the only male in our series, had alterations of the nails and tongue since childhood. Cultures from the under surface of his nails and from his tongue showed fungi—Trichophyton in the former and Candida in the latter. He had probably suffered from parathyroid insufficiency since the age of 16, since he first complained of numbness of his fingers at that time. He had two spontaneous nocturnal epileptic episodes. A seizure induced during hyperventilation showed loss of consciousness, sudden falling and generalized tonic convulsions. He also had a posterior cortical cataract.

On April 28, 1944, his total plasma calcium was 8.6 mg., ionized calcium 3.3 mg., inorganic phosphorus 6.86 mg. and total protein 8.45 Gm. *EEG I:* the electroencephalogram showed a 10 c/s alpha rhythm predominating throughout the cortex. In the frontal region there were occasional 2.5 c/s slow waves and also spikes. During hyperventilation occipital spikes occurred, some with a saw-tooth appearance, at an amplitude up to 100 microvolts.

Case 3, M. G., female, aged 40 years. This patient had a thyroidectomy for exophthalmic goiter on July 8, 1944. On the following day she developed symptoms of tetany.

On July 18, 1944, the total calcium in her plasma was 6.5 mg.; ionized calcium 2.8 mg., inorganic phosphorus 5.61 mg. and total protein 6.25 Gm. *EEG I*: the electroencephalogram showed a typical alpha rhythm of 11 c/s in the parieto-occipital region and a slower rhythm of 7 to 8 c/s in the frontal region. In the frontal region, during hyperventilation, the rhythm index[2] of 7 to 8 c/s increased and the potential of these waves rose up to 75

[2] Index is the percentage of time occupied by a rhythm in a record.

microvolts. Five minutes after the injection of calcium the record had resumed its original appearance. Subsequent hyperventilation produced an effect similar to that seen before the administration of calcium.

On December 5, 1944, the total calcium in plasma was 9.0 mg., ionized calcium 3.6 mg., inorganic phosphorus 4.11 mg. and total protein 8.49 Gm. *EEG II:* the sole difference between this electroencephalogram and the previous one was that the frontal slow rhythm was not in evidence and although it appeared after hyperventilation, the wave amplitude was somewhat smaller than in the first electroencephalogram. Injection of calcium, followed by a repetition of the hyperventilation, gave rise to the same effects noted in July.

Case 4, R. D., female, aged 23 years. Her brother had convulsive seizures followed by amnesia and was sent to a hospital for mental disorders. The patient had a thyroidectomy for exophthalmic goiter on April 23, 1946. The next day she developed the first manifestations of tetany. A fortnight later she suddenly lost consciousness for a few minutes. This was followed by upper conjugate movement of the eyes. It was noted that her tongue protruded to the left and was bitten severely. Later she had similar attacks during sleep.

On May 21, 1946, the total calcium in plasma was 6.2 mg., ionized calcium 2.2 mg. and total protein 9.25 Gm. *EEG I:* the electroencephalogram showed a pathological slow rhythm of 4.5 to 8 c/s with a maximum amplitude of 100 microvolts. This rhythm appeared in 2–3 wave bursts, arising in the frontal zone and spreading backwards toward the occipital region (Fig. 1—monopolar lead). During hyperventilation there were slow

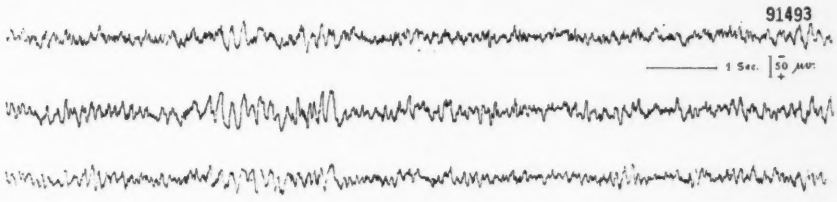

FIG. 1. Electroencephalogram in Case 4 on May 21, 1946 (plasma calcium 6.2 mg.).

waves of 2.5 c/s and an amplitude of 80 microvolts. The injection of calcium and further hyperventilation gave rise to no outstanding changes.

On March 22, 1947, the total calcium in plasma was 8.8 mg., ionized calcium 3.7 mg. and total protein 7.68 Gm. Since May 1946, the patient had had five more attacks of "petit mal." During the ten months following her first electroencephalogram she was supposed to have been taking 4 mg. of calciferol daily but she was very unfaithful in this regard and omitted it

entirely in the three weeks preceding her visit. *EEG II:* the electroencephalogram was identical with the previous one.

Case 5, R. B., female, aged 37 years. The patient had a thyroidectomy for colloid goiter on May 24, 1939. Tetany appeared a few hours after the operation and persisted until 1943. In that year she became pregnant and her symptoms improved a great deal. After delivery, tetany reappeared and in March, 1944, she suddenly lost consciousness and fell. She showed generalized clonic convulsions, urinary incontinence and frothing at the mouth. This state lasted for fifteen minutes and was followed by amnesia. It recurred two weeks later.

On April 16, 1944, the total calcium in plasma was 6.6 mg., ionized calcium 2.7 mg., inorganic phosphorus 6.8 mg. and total protein 6.93 Gm. *EEG I:* the electroencephalogram showed a rapid rhythm interrupted by paroxysms of 5 c/s abnormal waves with an amplitude up to 120 microvolts and lasting as long as four seconds. Between these waves, at intervals, there were fast spikes with an amplitude up to 140 microvolts. This phenomenon seemed to affect the entire cortex and it appeared to have a practically simultaneous onset, as shown in Figure 2. The character of the

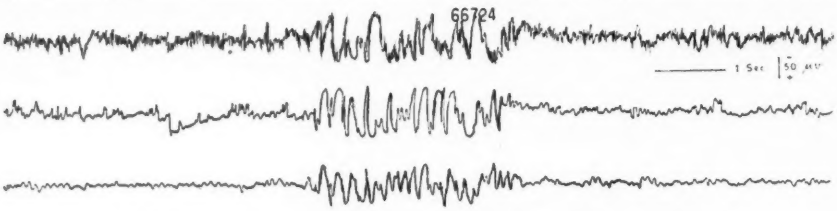

FIG. 2. Electroencephalogram in Case 5 on April 16, 1944 (plasma calcium 6.6 mg.).

paroxysms was similar to that seen in "petit mal." It should be noted that during the recordings the patient had only one muscular cramp.

On May 24, 1944, the total calcium in plasma was 8.8 mg. *EEG II:* the electroencephalogram had the basic features of the previous record, without the paroxysms. Hyperventilation caused no change.

On June 1, 1944, the total calcium in plasma was 10 mg., ionized calcium 4.3 mg., inorganic phosphorus 5.8 mg. and total protein 7.38 Gm. *EEG III:* the electroencephalogram showed the same basic rhythm as before. After hyperventilation a few isolated abnormal waves appeared.

On October 10, 1944, one month after calciferol has been omitted, the total calcium in plasma was 7.4 mg., ionized calcium 2.8 mg., inorganic phosphorus 6.72 mg. and total protein 8.35 Gm. *EEG IV:* the electroencephalogram showed the same basic characteristics as seen in EEG's I, II and III. Preliminary hyperventilation and then injection of calcium brought about no changes; but during the hyperventilation following calcium administration, there was a typical paroxysmal discharge. This

was more distinct in the midparietal area and had a frequency of 5 c/s with a maximum amplitude of 100 microvolts.

On August 29, 1946, after five months of calciferol therapy, the total calcium in plasma was 9.5 mg., ionized calcium 3.5 mg., inorganic phosphorus 4.4 mg. and total protein 9.24 Gm. *EEG V:* the electroencephalogram again showed no change. There were a few scattered groups of slow waves (5 to 6 c/s) running from the frontal to the occipital regions. These became more pronounced during hyperventilation.

Case 6, L. T., female, aged 26 years. The patient had undergone a thyroidectomy for exophthalmic goiter on May 5, 1940. On the same day she developed symptoms of hypoparathyroidism. She obtained transient relief from a parathyroid graft in the tibial bone marrow, four months after the thyroidectomy. A bone homograft performed later, also brought about short-lived relief.

On February 16, 1944, the total calcium in plasma was 5.6 mg., ionized calcium 2.2 mg., inorganic phosphorus 6.83 mg. and total protein 7.79 Gm. *EEG I:* the electroencephalogram showed an 8 c/s basic alpha rhythm with occasional bursts of 3 c/s slow waves, appearing only in the frontal region and having a maximum amplitude of 70 microvolts, for periods up to ten seconds.

On April 18, 1944, the total calcium in plasma was 11.4 mg., ionized calcium 5.6 mg., inorganic phosphorus 5.62 mg. and total protein 8.07 Gm. *EEG II:* the electroencephalogram remained unchanged.

On July 26, 1944, the total calcium in plasma was 9.3 mg., ionized calcium 4.3 mg., inorganic phosphorus 4.0 mg. and total protein 6.38 Gm. *EEG III:* in the initial period, this electroencephalogram was similar to the previous one, except that the index of the 3 c/s was smaller. Eighty seconds after starting hyperventilation there was a discharge of potential lasting for one second and composed of 5 c/s waves with an amplitude of 100 microvolts. These originated in the frontal region and spread throughout the cortex (Fig. 3). A fundamental alpha rhythm similar to that in the other

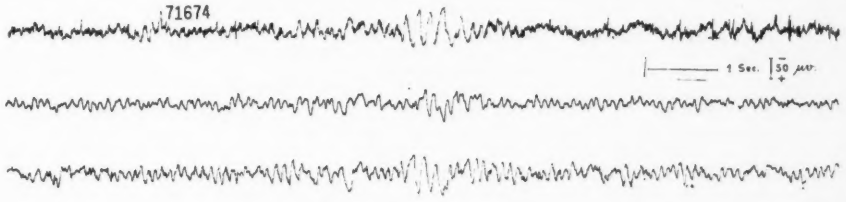

FIG. 3. Electroencephalogram in Case 6 on July 26, 1944 (plasma calcium 9.3 mg.). The illustration reproduces part of EEG III, taken during hyperventilation.

electroencephalograms was evident. After the injection of calcium the record resumed its previous appearance. Hyperventilation after the injec-

tion brought about changes similar to those appearing before the administration of calcium. This was followed by typical muscle-action potentials[3] lasting as long as seven seconds (Fig. 4).

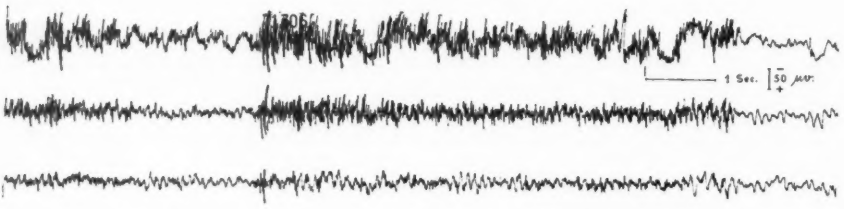

FIG. 4. Electroencephalogram in Case 6 on July 26, 1944, after injection of calcium and after hyperventilation had ended. There are typical muscle potentials.

On May 29, 1945, calciferol had been omitted for nine months. The total calcium in plasma was 7.4 mg., ionized calcium 2.7 mg., inorganic phosphorus 4.43 mg. and total protein 8.14 Gm. *EEG IV:* the electroencephalogram showed the same basic pattern as in EEG I but the characteristic slow waves were absent. During hyperventilation a few slow waves of 6 c/s appeared. Injection of calcium caused no change in this electroencephalogram and further hyperventilation reproduced, though on a smaller scale, the conditions found before the administration of calcium.

Case 7, S. K., female, aged 40 years. On August 12, 1941, the patient had a thyroidectomy for cystic goiter and a few days later she developed symptoms of tetany. In November she had an attack of generalized tonic convulsions with loss of consciousness, falling to the right, tongue biting and incontinence of urine. This episode lasted for ten minutes and was followed by amnesia. Since then she has suffered alternate episodes of tetany and epilepsy.

On February 10, 1944, the total calcium in plasma was 5.5 mg., ionized calcium 2.3 mg., inorganic phosphorus 6.8 mg. and total protein 7.07 Gm. *EEG I:* the electroencephalogram had a fast rhythm of 20 to 25 c/s, alternating with brief stretches of alpha rhythm, 9 c/s. There were also spikes and scattered waves (6 to 7 c/s) of an amplitude of 40 microvolts, more noticeable in the frontal region.

On March 17, 1944, the total calcium in plasma was 9.5 mg., ionized calcium 4.3 mg., inorganic phosphorus 4.29 mg. and total protein 6.93 Gm. *EEG II:* this electroencephalogram was similar to EEG I.

By August 1, 1944, calciferol had been omitted for one month. The total calcium in plasma was 6.2 mg., ionized calcium 2.6 mg., inorganic phos-

[3] Muscle potential following hyperventilation is very common in normal electroencephalograms. It is produced by the patient swallowing, in order to moisten pharyngeal passages dried by the overbreathing.

phorus 3.7 mg. and total protein 7.11 Gm. *EEG III:* the electroencephalogram showed the initial part of the record similar to the two previous ones. In the frontal region, during hyperventilation, there were slow waves of 4 to 5 c/s. After hyperventilation, the patient developed a severe generalized attack of tetany identical to the spontaneous one she had had previously. While this attack was in progress the electroencephalogram remained unchanged except for the appearance of generalized discharges of muscle-action potentials. After the injection of calcium the recording showed features identical to those appearing before the injection but without the muscle discharges. Owing to technical difficulties, eight minutes elapsed between the injection and the resumption of the electroencephalogram.

On November 21, 1944, the total calcium in plasma was 12.4 mg., ionized calcium 5.0 mg., inorganic phosphorus 4.35 mg. and total protein 8.38 Gm. *EEG IV:* the electroencephalogram was similar to the first one in its basic features. During hyperventilation it retained all the previous characteristics, except that the discharges of muscle-action potentials reappeared. These disappeared after the injection of calcium.

Case 8, A. C., female, aged 35 years. The patient had a thyroidectomy for exophthalmic goiter on September 23, 1933. Ten days later she developed symptoms of tetany which persisted. In 1937, the patient had a severe erythrodermatitis of unknown origin. A few months later her behavior became abnormal and a psychiatrist (Dr. Thénon) made a provisional diagnosis of manic psychosis, with delusions of persecution and episodes of confusion and hallucinations.

On September 24, 1944, the total calcium in plasma was 5.2 mg., ionized calcium 2.0 mg., inorganic phosphorus 4.79 mg. and total protein 8.06 Gm. *EEG I:* the recording of the electroencephalogram was difficult because of the unusually high resistance of the scalp. When placed in their usual locations, the electrodes showed resistances of 100,000 ohms (frontal), 300,000 ohms (parietal) and 250,000 ohms (occipital). This was perhaps due to the erythrodermatitis the patient had had seven years previously. Needles passed into the scalp overcame this difficulty and the resistance was reduced to 18,000, 2000 and 15,000 ohms respectively. The electroencephalogram of the frontal region showed only potentials due to movement of the eyelids. In the parietal and occipital regions there was an alpha rhythm of very small amplitude—14 microvolts. One minute of hyperventilation brought about no changes.

RESULTS

THE ELECTROENCEPHALOGRAM IN NORMAL FEMALES

Four normal female students were used for controls. Total plasma calcium values ranged between 9.4 and 10.2 mg.; ionized calcium, between 3.8 and 4.2 mg.; inorganic phosphorus, between 2.50 and 4.22 mg.; and total

protein, between 7.42 and 8.11 Gm. In all cases the initial electroencephalogram appeared normal. During hyperventilation there were no changes, although one patient showed discharges of muscle-action potentials in the occipital region. The injection of calcium and the hyperventilation which followed brought about no alterations.

THE ELECTROENCEPHALOGRAM IN HYPOPARATHYROIDISM

During hypocalcemia and tetany: Twenty-two electroencephalograms taken in the 14 cases of tetany showed a predominance of alpha rhythm with an average frequency of 10 c/s in 8 cases, and a fast rhythm with frequencies over 20 c/s in 6 cases.

A more careful analysis revealed that in most of the records there were slow waves of varying frequency, from 2 to 5 c/s. Almost the entire record in Case 4 was composed of slow waves (Fig. 1). In other cases these waves appeared alternating with the basic rhythm for stretches lasting up to ten seconds. More often they occurred in series of 3 to 4 waves, or were isolated. These slow waves were sometimes generalized but usually localized. When localized, they appeared in the frontal region. Only one patient showed them in the occipital area. In the generalized type, the waves appeared in the frontal lobe and spread to the parieto-occipital areas. The exception was found in the record illustrated in Figure 2, in which the waves apparently began in the parieto-occipital area.

Another feature was the spikes which were present in 5 cases. Those in Case 5 (Fig. 2) appeared in bursts throughout the cortex, interspersed with slow waves. In the other patients they occurred as isolated localized entities, showing no preference for a given cortical area. Rarely were spikes and slow waves found together in any one case.

The effects of hyperventilation were studied in 10 cases. This resulted in minimal alterations but isolated slow waves, with or without spikes, occurred in cases in which they did not exist before. If these slow waves had existed previously, hyperventilation sometimes increased their index or amplitude. These changes could last until the effects of hyperventilation had worn off.

In the 6 patients studied, the intravenous injection of calcium had no definite effect on the electroencephalogram. When the calcium was injected before the effects of hyperventilation had worn off, there was no sudden change in the abnormalities in the electroencephalogram. Therefore, one must be careful not to attribute to the effect of calcium, changes which would have occurred spontaneously.

Hyperventilation carried out after calcium was injected resulted in changes similar to those seen in hyperventilation before calcium was injected. This means that the injection of calcium does not prevent the onset of slow waves caused by hyperventilation. On the contrary, in Case 5, we

observed 5 c/s paroxysmal discharges during hyperventilation after calcium administration: whereas there were no changes during hyperventilation before calcium administration. It would seem that the first hyperventilation had augmented the effect of the second.

During normocalcemia: In the 8 cases of tetany in which the encephalograms were recorded when the values for total plasma calcium were normal, the basic rhythm was either alpha or fast—the same as when the values for plasma calcium were subnormal. However, the slow wave index appeared to be lower in general. Hyperventilation followed by the injection of calcium and subsequent hyperventilation, produced effects similar but less definite than those observed in hypocalcemia. These differences can be seen clearly in Case 5: during hypocalcemia without hyperventilation, the patient showed spontaneous bursts of slow waves and spikes. Her electroencephalogram taken during normocalcemia showed a few isolated abnormal waves only after hyperventilation.

During hypercalcemia: The 3 patients whose records were made while plasma calcium levels were above normal (11.4, 11.8 and 12.4 mg.) showed unchanged basic rhythms. In 2 of the patients whose records had previously shown slow waves, no electroencephalographic changes were noted

DISCUSSION

The patients investigated in this study presented all types of hypoparathyroidism. Eleven were of the more common postoperative variety and 3 were idiopathic. There were 2 postoperative patients in whom the disease was of recent onset, namely, ten and thirty days previously, respectively. In the other patients it was of long standing—from three to fourteen years. There were some latent or mild cases, some severe cases and a wide range of intermediate types. The prevalent signs and symptoms were tetany, epilepsy, psychosis and trophic changes. The values for calcium in plasma varied from very low figures (such as 5.2, 5.5, 5.6 mg.) to figures just below normal (8.4, 8.5 mg.). The corresponding values for inorganic phosphorus ranged between 6.83 and 4.36 mg.

Our results show that in tetany the basic electroencephalogram rhythm, whether alpha or fast, retains all the individual characteristics which it possessed before the parathyroid insufficiency, regardless of the plasma calcium level or the clinical condition of the patient.

The most frequent and striking abnormality of the electroencephalogram in parathyroid insufficiency is the 2–5 c/s slow waves. The occurrence of spikes is a minor feature. Slow waves appear either singly or in series. They are seldom found throughout the record. These waves are usually localized to the frontal region and are less often observed throughout the cortex. Hyperventilation intensifies this characteristic. An intravenous injection

of calcium has no effect on the abnormalities in the record, i.e., it does not eradicate the slow waves or spikes or decrease their index.

Slow waves: In the investigation of the possible source of the slow waves we considered:

a) *The duration of the disease.* The slow wave index was so high in one of the cases of recent onset that the waves practically covered the entire record. Conversely, in several longstanding cases of parathyroid tetany the slow waves were very scarce. It appears, therefore, that the duration of the disease does not influence the incidence of slow waves.

b) *Plasma calcium level.* Broadly speaking, the slow wave index appears to be greater in patients with very low values for plasma calcium (lower than 6.6 mg.) than in those with only a slightly subnormal value (8.4 mg.) There are some exceptions, however, since in certain instances slow waves were not found when the level of plasma calcium was low. When comparing the electroencephalograms of any one patient, we found, with only one exception, that the slow wave index was higher during hypocalcemia than during normocalcemia or hypercalcemia. Therefore, there seems to be a correlation between the plasma calcium level and the slow waves. We must bear in mind, however, that slow waves can persist in patients in whom the values for plasma calcium have been raised to normal levels; and that the administration of calcium intravenously is not followed by a decrease in the slow waves. Perhaps the process in the innermost depths of the cerebral tissue which gives rise to the slow waves may not be affected by sudden and fleeting increases of blood calcium, such as those caused by intravenous injection, but is influenced only when the blood calcium level remains consistently normal, as during calciferol therapy.[4] It cannot be stated definitely that the calcium level is the sole determining factor of slow waves in the electroencephalogram of parathyroid insufficiency.

c) *Possible existence of the slow waves before the onset of hypoparathyroidism.* This might be the situation in Case 4. In this patient the dysrhythmia was discovered a few days after the onset of postoperative tetany. It was still present when the plasma calcium level became practically normal (8.8 mg.). Predisposing circumstances, whether congenital or acquired, cannot be ruled out entirely.

From the evidence available, there seems to be a causal relationship between hypocalcemia and the onset of slow waves. However, other factors, which we have been unable to identify, must be involved.

The discharges of muscle-action potential are not true electroencephalographic phenomena. Their characteristic appearance is illustrated in Figure 4. They always appeared in the record during or after hyperventilation, their presence coinciding with the onset of symptoms of tetany, such

[4] We infer that the concentration of calcium in the brain cells must undergo variations similar to those which occur in the blood stream.

as carpal spasms. Depending upon which muscle group was contracted, these discharges were more prevalent in the occipital or in the frontal leads. They are merely electroencephalographic manifestations of tetany, not necessarily subordinated to hypocalcemia. They were present in the electroencephalograms of control subjects and they were no more prevalent in instances of severe hypocalcemia. The discharges seen in Figure 4 belong to the record of a patient (Case 6) with a normal blood calcium level. They appeared after the hyperventilation that following the injection of calcium. In Case 7 the patient had hypercalcemia and showed the most typical muscle potential. Alkalosis is the determining or decisive factor in these discharges.

Relationship of tetany to epilepsy: Epilepsy appears relatively frequently during the course of parathyroid insufficiency. Of our 14 patients, 5 and possibly 6, gave a history of "fits." There was a remarkable difference between the incidence of epilepsy in the cases with idiopathic tetany and those with postoperative tetany. In our 3 cases of spontaneous tetany, 2 and possibly 3, had had previous convulsions. This was true in only 3 of the 11 postoperative cases. In Case 4 the tetany occurred on the first day after thyroidectomy and the epileptic fits began a fortnight later. The electroencephalogram showed a continuous and generalized gross dysrhythmia characterized by slow waves predominating throughout the record. In Case 5, however, the patient had her first seizure five years after the onset of postoperative tetany and typical paroxysms of slow waves and spikes can still be seen in her electroencephalogram. When these paroxysms were recorded there were no accompanying clinical manifestations. They were true subclinical attacks, revealed only by the electroencephalogram.

From our data, it may be seen that in parathyroid epilepsy the electroencephalogram may show: a) characteristics so definite that through them alone a diagnosis of epilepsy can be made (Case 5); patterns which show only the existence of a dysrhythmia, which may or may not have been present previously (Case 4); and c) a normal or only slightly abnormal record with few slow waves or spikes, even after hyperventilation. Similar patterns may be present in epilepsy from other causes: therefore, the electroencephalogram in parathyroid insufficiency is not specific

Sustained large doses of calciferol eliminated the symptoms of tetany and the clinical manifestations of epilepsy. In Case 5 successive electroencephalograms did not show the typical bursts of the first one, even with hyperventilation. Since calciferol therapy is not substitution therapy, the benefits derived from its administration cannot be attributed to the disappearance of the disease and must be ascribed to its action in increasing the level of calcium in the blood. By inverse reasoning we can conclude that hypocalcemia is an essential pathogenic factor of parathyroid epilepsy and of its eventual electroencephalographic changes.

As in the case of the slow waves, the duration of hypoparathyroidism is not a factor in the onset of epilepsy, since epilepsy can become clinically manifest either a few days or several years after the onset of tetany. Moreover, there are many patients with longstanding tetany who never become epileptic. Presumably, parathyroid insufficiency *per se* cannot cause epilepsy: a predisposing or assisting factor is required. Epilepsy in parathyroid insufficiency seems to result from hypocalcemia acting in a predisposed subject.

SUMMARY

During hypocalcemia, 22 electroencephalograms in 14 cases of tetany showed a predominance of alpha rhythm in 8 cases and a fast rhythm in 6 cases. Muscle action potentials were sometimes a prominent feature.

The most striking abnormality in the electroencephalogram of parathyroid insufficiency is the occurrence of slow waves (2–5 c/s), either singly or in series, with occasional spiking. Hyperventilation enhances them. An intravenous injection of calcium has no effect on them but they tend to disappear if the blood calcium is restored to the normal level by calciferol therapy. Hypocalcemia seems to be the conditioning factor for their appearance.

Epilepsy is frequently associated with parathyroid insufficiency. Under these conditions the electroencephalogram may show: a) typical bursts of slow waves and spikes; b) continuous generalized dysrhythmia; c) slow waves, either single or in series; or d) a normal record.

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DIABETES MELLITUS FOLLOWED BY ADDISON'S DISEASE AND HYPOTHYROIDISM, SIMULATING PANHYPOPITUITARISM

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IN 1938 Bloomfield (1) reported a unique, unequivocal case of coincidental diabetes mellitus and Addison's disease. The same case again appeared in the literature in 1944, when Armstrong (2) reported the effect of testosterone on this patient's condition. Since the last report, the clinical picture of hypothyroidism in this patient became more striking, and finally a diagnosis of panhypopituitarism was made.

The present paper will summarize briefly the clinical course and interval history since last reported, and present the autopsy findings.

CASE HISTORY

A 35-year-old American electrician first entered Stanford University Hospital, April 18, 1938, complaining of weakness and weight loss of 18 pounds in two months.

One sister died of diabetes mellitus at the age of 18 years, and a niece at the age of 3 years. The rest of the family history was not pertinent.

In March of 1938, there was a sudden appearance of increased thirst and polyuria. At this time physical examination of the patient was not remarkable; his weight was 49 kilograms and his blood pressure was 120/75. There was sugar, diacetic acid and acetone in the urine, and the blood sugar was 560 mg. per cent. Diet and 56 units of insulin per day restored his blood sugar to a normal level. After an interval of well-being with fair control of his diabetes, he experienced an insulin reaction in December 1938. Because of subsequent reactions his insulin was eventually reduced from 40 to 4 units once or twice daily.

In March 1939, although his urine was sugar-free, he became weak, exhausted, craved salt, and his skin commenced to become yellow-brown. He re-entered the hospital in May, 1939. At this time his blood pressure was 85/60, blood chloride 385 mg. per cent, blood urea 57 mg. per cent, and basal metabolic rate minus 15 per cent. His blood sugar during fasting was 105 mg. per cent, and there was only a trace of sugar in his urine. A biopsy of his skin revealed no evidence of hemochromatosis. There was marked clinical improvement during the administration of sodium chloride, suprarenal cortex extract and desoxycorticosterone acetate. The cortical extract alone produced hyperglycemia and glycosuria (2).

During the next seven years the patient had ten more hospital entries. In January and July of 1940, he re-entered because of hypoglycemic reactions. At the time of the latter entry his blood sugar was 54 mg. per cent, and his basal metabolic rate was minus 25 per cent. His condition was brought under control with 2 units of insulin, 8 grams of sodium chloride by mouth and 2 mg. of desoxycorticosterone acetate intramuscularly. He was soon feeling well enough to work forty hours per week.

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When he entered in January 1942, he complained of decreased tolerance to cold. At the time of this entry he had an anemia with 77 per cent hemoglobin and 3.3 million red blood cells. His urine was not remarkable. His blood sugar was 130 mg. per cent and blood chloride, 510 mg. per cent. The basal metabolism was minus 42 per cent.

In July 1942, he was puffy, cold, extremely lethargic and his basal metabolic rate was minus 51 per cent. Blood sugar determinations ranged from 35 to 114 mg. per cent. Plasma chloride was 528 mg. per cent. Ten cc. of suprarenal cortex extract increased appetite and activity and raised the blood sugar to 440 mg. per cent. The urinary 17-ketosteroid excretion was 4.2 mg. per twenty-four hours. Sperm counts were normal. Desiccated thyroid was prescribed in a dose of one-half grain daily, in addition to desoxycorticosterone acetate (0.8 cc. intramuscularly daily), sodium chloride (10 Gm. by mouth daily) and insulin (4 units every other day as needed).

During the course of the next year he lost 22 pounds and was again hospitalized in August 1943. At the time of this entry his basal metabolic rate was minus 29 per cent but his blood sugar, blood urea and blood pressure determinations were normal. Roentgenograms of the skull showed no changes in the sella turcica. An insulin tolerance test had to be terminated in two hours because of marked hypoglycemia. Following three daily injections of 25 mg. of testosterone propionate there was rapid increase in vigor and appetite, the caloric intake rose from 1100 to 1600 calories per day and hyperglycemia ensued (2).

During his last three years there were repeated hospital entries due to hypoglycemia; and with each entry, progressive mental deterioration was observed. Finally, on February 16, 1947, he was admitted in a semicomatose condition and died the following day.

AUTOPSY FINDINGS

Gross Examination

The autopsy was performed five hours after death. The body was that of an emaciated man, 5 feet 9½ inches tall, weighing approximately 50 Kg. There was generalized brown pigmentation of the skin, most marked over the face and sparing the medial aspects of the thighs and legs. There was very little subcutaneous fat which averaged only 3 mm. in thickness over the thorax and abdomen.

The viscera generally, were rather small. This was most striking in the endocrine glands. No remnant of either adrenal gland was identified. In their place was found a small amount of deep yellow perinephric fat at each kidney pole. This in places was distinctly brown but had the lobular structure of adipose tissue. Macroscopically, nothing was found that suggested the adrenal capsule. Zenker fixation revealed no brown-stained areas that could have been interpreted as medullary tissue. Diligent search for aberrant adrenal cortical tissue on the inferior surface of the liver, beneath the renal capsule, along the ventral surface of the aorta, along the spermatic cords and in the testes and epididymes, was also unproductive.

The pancreas, although unusually small, showed normal lobulations and a normal cut surface. It weighed 14.0 Gm.

The thyroid gland was extremely small (5.0 Gm.), white, and unusually firm when cut. Four parathyroid glands were found without difficulty and although grossly normal, had a combined weight of only 0.052 Gm.

The pituitary gland was removed by careful dissection since, clinically, the diagnosis of panhypopituitarism was entertained. However, this gland was not remarkable grossly and the anterior lobe weighed 335 mg.

The testes were normal in size and texture. The prostate, although slightly small,

was otherwise not remarkable. No thymus was identifiable grossly, and there was no generalized lymphoid hyperplasia.

The heart weighed 210 grams. The coronary arteries showed atheromatous plaques which occluded the vessels in a few places. A white fibrous area, 3 × 2 cm., represented the site of old infarction at the left ventricular apex.

The lungs weighed 500 grams each, and the left presented many fibrous adhesions. There were bilateral, pearly, apical, pleural scars with very small fibrous parenchymal scars beneath them. There were no calcified foci in either the lung parenchyma or the hilar nodes.

The remainder of the organs were not remarkable, save for their somewhat small size (liver 880 Gm., spleen 55 Gm.). Dissection of the brain after formalin fixation revealed a brown glistening area in the left pons; the rest of the organ was not remarkable.

Microscopical Examination

Adrenal Glands: Unequivocal cortical cells were found only after multiple sections of the perinephric fat were made. No adrenal tissue was found on the left. On the right, two remnants which measured 2 × 2 × 1 mm. each, composed all of the adrenal tissue that could be found. The cells were very small, occurring in clumps and strands, the latter occasionally simulating the fascicular arrangement of the adrenal cortex, but with increased fibrous tissue. There was no evidence of focal compensatory hypertrophy of the remaining cortical cells. The rest of the adrenal gland was represented by only the fibrous capsule which appeared to be of normal thickness. The layers of capsular fibrous tissue were separated by a narrow space containing pre-existing blood channels and a few scattered lymphocytes (Fig. 1). No evidence of former disease was found in either the adrenal remnants or the periadrenal fatty tissue. There was no evidence of vascular occlusion. Cells of the medulla were not definitely identified.

Pancreas: The secreting cells seemed normal morphologically, but uniformly smaller than are usually seen. Islets were plentiful, but were composed of small cells with round, densely stained nuclei, and little cytoplasm (Fig. 2). There was no fibrosis or hyalinization. A differential stain for pancreatic islet cell types, according to Gomori (3, 4), revealed that the predominant cell was agranular, probably of the D type. Alpha cells were easily recognizable, but only a few unequivocal beta cells were present. The ratio of beta to alpha cells was approximately 1 to 50 (normal range 3–8 to 1).

Thyroid Gland: Dense fibrous tissue with scattered lymphocytes and large aggregates of lymphoid tissue, replaced the usual glandular structure (Fig. 3). The largest acinus found after perusal of several representative sections, was approximately 0.5 mm. in diameter. Occasional clumps of small (50 micra) acini lined by cuboidal epithelium were seen. Some of these acini contained a pink amorphous material which resembled colloid. Hyperplastic arteries with hyalinized intimae and occasional intimal calcification, were not infrequent.

Parathyroid Glands: The cellular component was unusually dense. These cells, as in the other organs, were small with scanty cytoplasm. The predominant cell was the dark chief cell. There was a paucity of oxyphils, which when present, occurred singly or in small clumps. "Water-clear" cells were not infrequent.

Hypophysis: The fibrous tissue was diffusely increased without evidence of broad scar formation. Not infrequently, the fibrous tissue separated clusters of anterior lobe cells from the capillary channels. The anterior lobe cells were uniformly small and closely packed. Well-granulated acidophiles were reduced in numbers, a change which was quite conspicuous in preparations stained with aniline-acid fuchsin. This was the most

FIG. 1. Right adrenal gland represented by fibrous capsule which borders branches of the suprarenal veins. Complete disappearance of cortex and medulla. Arrows indicate the layers of capsular fibrous tissue (×120).

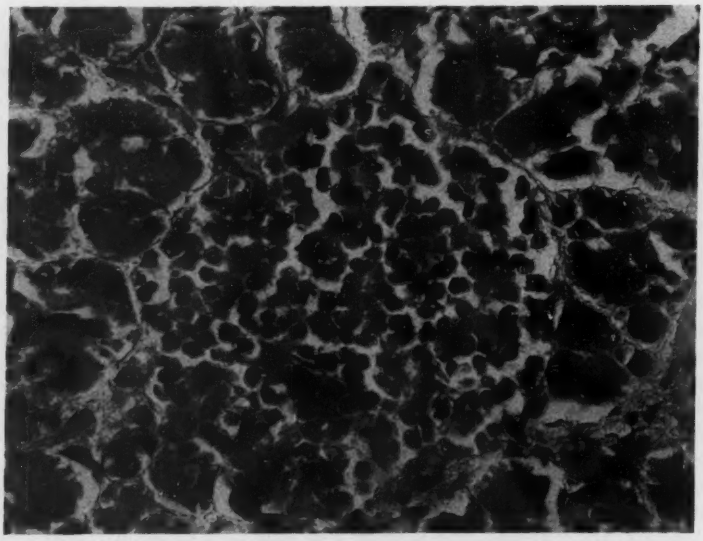

FIG. 2. Section of pancreas showing an islet in center (Gomori preparation, ×220).

FIG. 3. Replacement of thyroid gland by fibrous and lymphoid tissue. Small thyroid acini are seen within the mass of lymphocytes (× 120).

FIG. 4. Testis, showing slight reduction in size of tubules. Germinal epithelium and interstitial cells normal (× 120).

important alteration next to the smallness of the cells and interstitial fibrosis.

Small granulated basophiles with vesicular or compact nuclei were scattered throughout the anterior lobe. Occasionally, the granular cytoplasm was replaced by a hyaline basophilic material and such cells usually had compact dark nuclei. The granulated basophiles were somewhat more numerous close to the posterior lobe junction. In Zenker-formalin fixed tissue stained with aniline-acid fuchsin methyl-green, short rodlike or globoid fuchsinophilic structures were seen in the cytoplasm of the basophilic cells which were suggestive of mitochondria.

Testes: The germinal epithelium and the interstitial cells were normal although a slight decrease in the size of the seminiferous tubules was noted (Fig. 4).

DISCUSSION

It is readily understandable that the progression of signs and symptoms in this patient led most of the attending clinicians to diagnose panhypophyseal deficiency, in addition to diabetes mellitus.

It is impossible to determine with certainty whether or not hypothyroidism and Addison's disease existed when the patient first entered as a diabetic. The clinical history suggests that the Addisonian state was subsequent to the diabetes mellitus. The strongest evidence for this belief is the fact that skin pigmentation and a progressive diminution in insulin requirement occurred nine months after the diabetes mellitus was first recognized. Although early in the course of the Addison's disease, a basal metabolic rate of minus 15 per cent was recorded, it is not certain that this actually signified thyroid deficiency. The later hypothyroid state, determined clinically and verified at autopsy, was obviously related to the replacement of the gland by lymphoid and fibrous tissue. Although lymphoid hyperplasia was present, the striking replacement by fibrous tissue was different from the changes usually found in chronic adrenal insufficiency. The diabetes mellitus was probably associated with the paucity of beta cells in the pancreatic islets, as there is good evidence that these cells are responsible for the secretion of insulin (4).

The pituitary picture in this case is not a typical finding in primary adrenal atrophy although diminution in cell size and increased fibrous tissue have been reported (5, 6, 7, 8, 9). The alterations in the anterior lobe basophiles, save for the absence of the large pale basophile or transitional basophile of Crooke (10), were similar to those observed in other cases. As suggested on a previous occasion (11), the decrease in well-granulated acidophiles may be related to the advanced state of thyroid replacement by lymphoid and fibrous tissue. It is of interest, therefore, that in an unreported case of primary atrophy that has been recently studied where the thyroid gland failed to show evidence of replacement by lymphoid tissue, the hypophysis contained significantly greater numbers of well-granulated acidophiles than seen in the case reported here.

In contrast to the points discussed thus far, the preservation of testicular structure and function cannot be overstressed. The presence of spermatozoa in the tubules and the normal appearance of the secondary sex organs are good evidence of pituitary activity. Moreover, the adrenal picture described does not resemble that seen after severe pituitary destruction. The disappearance of the adrenal cortex favors the concept of cytotoxic dissolution (7, 13, 14).

SUMMARY

A clinical case of diabetes mellitus ameliorated by Addison's disease, and further complicated by hypothyroidism is presented. The autopsy revealed that the sequence of events was not explainable on the basis of a primary hypophyseal deficiency.

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FERTILITY AND DYSGERMINOMA OVARII

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From the Department of Obstetrics and Gynecology, Cornell University Medical College and The New York Hospital

PREGNANCIES have occurred in the presence of or after the removal of dysgerminomata. The harborers of these rare ovarian tumors, which are usually on the right side, are not necessarily sterile. These patients may be grouped into those with normal pelvic organs and secondary sex characteristics; and those who have coincidentally undeveloped genitalia or pseudohermaphroditism. All of the pregnancies reviewed have been in the former group. The incidence is 1 in 43,822 deliveries at the Woman's Clinic of the New York Hospital.

Most unusual are some of the circumstances in which the pregnancies have occurred. Lorber (1) reported a patient whose tumor was diagnosed in the third month of gestation. A corpus luteum of pregnancy was found in the capsule of the tumor. Cunningham (2) delivered a healthy infant by cesarean section from a patient with large, bilateral ovarian tumors and widespread metastases. This patient succumbed fourteen months later. Von Szathmary (3) reported a case with a fist-sized cold abscess in the left adnexal region and a large ovarian tumor in the right. At laparotomy six weeks postpartum, a dysgerminoma was found on the right and a tuberculous abscess on the left. Doubrère's (4) patient developed intestinal obstruction due to such a tumor eight days after delivery.

Seegar (5) tabulated 98 cases showing an over-all fertility of 23 per cent as indicated by known pregnancies. His series includes patients of all ages and sexual development in whom pregnancy occurred before, concurrently with, or after removal of the tumor. Since the tumors are presumably neutral and neither masculinize nor exaggerate the feminine characteristics, a reasonably high fertility may be expected in those patients with unilateral tumors in whom there is no genital hypoplasia. It would appear that the tumor causes sterility in normal females only in so far as it destroys or displaces ovarian tissue or causes tubal occlusion by mechanical pressure. In Novak's (6) series of 17 cases the oldest patient was 38 years of age.

The 39-year-old patient reported here became pregnant within one year after her marriage and twelve years after removal of the tumor by surgery which had been followed by prophylactic x-ray treatment.

CASE REPORT

Mrs. M.D., No. 462780, aged 39 years, an elderly primigravida, registered in the antepartum clinic of the Woman's Clinic of the New York Hospital on December 4, 1946.

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Her last menstrual period was October 1, 1946. She was then in the ninth week of her pregnancy with an expected date of confinement of July 8, 1947. The past history was remarkable in that her right tube and ovary had been removed in 1934. Menstruation began at the age of thirteen with a 25-day cycle lasting seven days, moderate flow and no dysmenorrhea. The patient married on October 27, 1945, and conceived within one year after her marriage. *Physical examination* revealed a well developed woman appearing somewhat younger than her chronological age. Temperature, pulse and respirations were normal. Her blood pressure was 116/76. There was a slight, diffuse, enlargement of the thyroid gland without exophthalmos or tremor. The heart and lungs were normal. The breasts were slightly engorged. The abdomen was symmetrical and the liver and

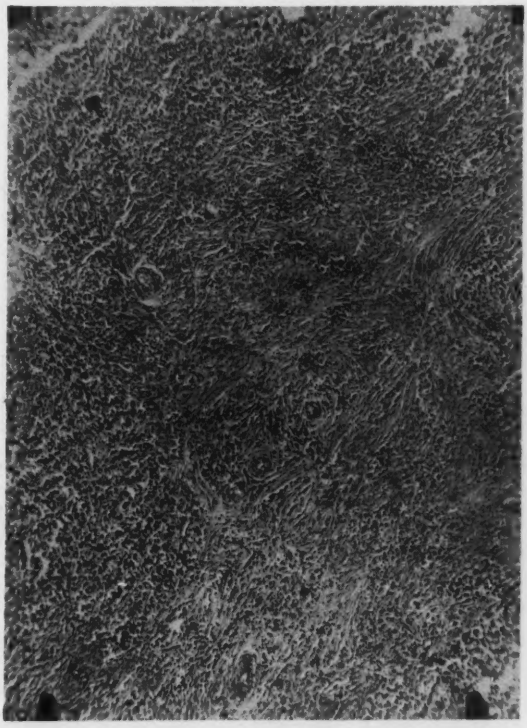

FIG. 1. Low power microphotograph showing nests and strands of cells with hyperchromic nuclei separated by connective tissue stroma.

spleen were not enlarged or tender. Pelvic measurements were normal. Vaginal examination revealed a uterus corresponding in size to the duration of pregnancy and no adnexal masses. Routine antenatal tests revealed normal urine; hemoglobin 95 per cent; and blood type, group A, Rh negative. X-ray examination of the chest showed normal lung fields with a normal cardiac outline. Her antepartum course was complicated by pyelitis due to B. coli in the twenty-seventh week. This infection responded promptly to sulfadiazine

therapy. On June 22, 1947, the membranes ruptured spontaneously and prematurely in the thirty-eighth week of pregnancy and labor started twenty-four hours later. The patient was delivered of a 2900 gram child by mid-forceps operation after thirteen hours and ten minutes of labor. The indication for the operation was a prolonged second stage due to a persistent occiput posterior position. The infant had a first degree hypospadias. Examination of the mother six weeks postpartum revealed a normal genital tract. The uterus was anterior in position and within the upper limits of normal in size. The left ovary was normal. The right adnexa were absent.

A résumé of the patient's illness in 1934, which was cured by salpingo-oophorocystectomy at another hospital reveals some unusual features.

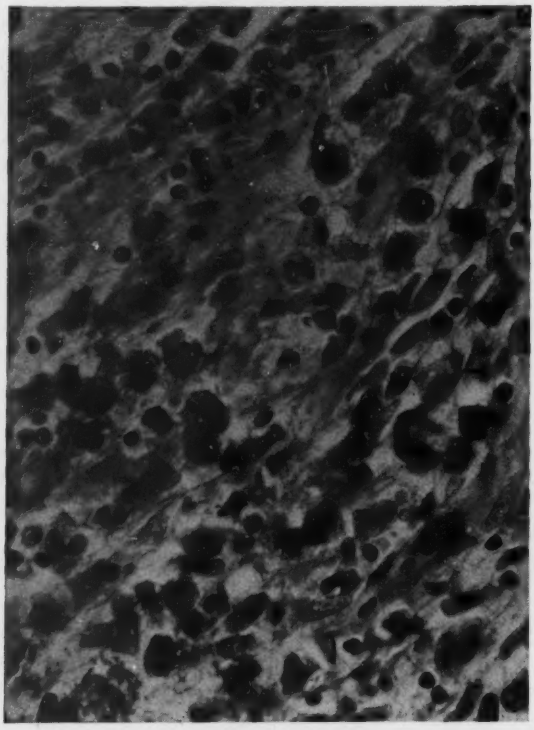

FIG. 2. High power microphotograph showing large, polyhedral, cells, many mitotic figures and characteristic infiltration with round cells.

At that time she had right lower quadrant pain and a sense of fullness in the abdomen. A tumor of the right ovary was felt on bimanual examination and at laparotomy there was free, bloody, fluid in the peritoneal cavity. The tumor was described as large, pearly-white in color, and well encapsulated. Figures 1 and 2 show the microscopic characteristics of the tumor.

Postoperatively the patient received four x-ray treatments. Three of these were through an anterior portal and one through a posterior portal. The therapist informed her that he was shielding the left ovary with a lead screen. The exact dose given is not known but presumably less than a castrating dose reached the left ovary since the patient menstruated regularly after the radiation.

TREATMENT

The possibility of subsequent pregnancies should be given consideration in the treatment of dysgerminoma, as these tumors occur most commonly in young women. If the tumor is unilateral, the capsule is intact, and the opposite ovary and tube are normal, a unilateral oophorectomy is indicated (7). Should bilateral tumors with or without extension be found, radical surgery is indicated followed by radiation. Conservative surgery should be followed by frequent examination for evidence of metastases or the development of a tumor in the remaining ovary. The anaplastic characteristics of carcinoma are of little aid in arriving at a decision as to whether the tumor is benign or malignant. In the case reported here a diagnosis of carcinoma had been made by the pathologist.

Dysgerminomata are said to be very radiosensitive. Moreton (8) advocates a moderate voltage, single dose method of treatment with a 130 Kv., 6 mm. Al filter. Four anterior portals are outlined extending from the xiphoid to the pubis and also four corresponding posterior portals. The left supraclavicular space is routinely irradiated. The surface of each field receives 540 r in air. This is repeated in one month. Subsequent x-ray therapy is dependent on the results of periodic examinations.

SUMMARY

The increasing number of case reports in which the patient has conceived prior to, in the presence of, or after excision of a dysgerminoma would seem to indicate that these tumors cause infertility only in so far as ovarian tissue is replaced or destroyed by the growth. A patient is reported in whom a dysgerminoma of the right ovary was removed by surgery which was followed by radiation therapy. Twelve years later, at 39 years of age, she gave birth to a full term child with mild hypospadias.

ACKNOWLEDGMENT

Dr. E. M. Burke of the Roswell Park Memorial Institute, Buffalo, New York, kindly provided us with the original slide of the tumor in this case.

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ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS ANNOUNCEMENTS

RECIPIENTS OF SQUIBB AND CIBA AWARDS AND AYERST, MCKENNA AND HARRISON FELLOWSHIP FOR 1948.

The Association for the Study of Internal Secretions has just announced that the award provided by E. R. Squibb and Sons has been conferred on Dr. Fuller Albright of Harvard Medical School, the award furnished by the Ciba Pharmaceutical Company has been made to Dr. Carl G. Heller of the University of Oregon College of Medicine, and the Ayerst, McKenna and Harrison Fellowship has been given to Dr. Ernest M. Brown, Jr., of the George S. Cox Medical Research Institute, University of Pennsylvania.

Doctor Albright, the recipient of the Squibb Award for 1948, has contributed greatly to our understanding of a variety of endocrine functions and dysfunctions in man. His studies on hyperparathyroidism and on calcium and phosphorus metabolism have been incorporated in modern textbooks on these subjects. He has extended this work by making important additions to our knowledge of bone metabolism and its endocrine control, the formation of renal calculi and certain renal disorders. In addition he has described the syndrome of osteitis fibrosa disseminata, pigmentation and endocrine dysfunction which bears his name and he has given us one of the best concepts of Cushing's disease through investigations which applied to this condition the modern ideas of adrenal cortical physiology. Almost every field of endocrine disease has been enriched by his work. Above and beyond this he has been a lucid teacher and a constant inspiration to all his fellow students of endocrinology.

Doctor Albright was born in 1900. He received the degree of Doctor of Medicine from Harvard University in 1924. He served as House Officer at the Massachusetts General Hospital, 1924–26; as assistant medical resident at the Johns Hopkins Hospital, 1927–28 and as Moseley travelling fellow, at Harvard, 1928–29. He was instructor and associate in medicine, Harvard Medical School, 1931–39; assistant professor, 1939–42; and associate professor of medicine, 1942 to the present, serving as physician to the Massachusetts General Hospital. He is past president of the American Society for Clinical Investigation and of the Association for the Study of Internal Secretions.

The Ciba Award for 1948 to Doctor Heller was given for his significant contributions to the study of the physiology of reproduction with particular

reference to disorders of reproduction in man. His studies have combined techniques of the endocrine laboratory with those of the medical clinic to advance diagnostic and therapeutic procedures in various forms of hypogonadism. Doctor Heller was born in Syracuse, N. Y. January, 1913. He received the degree of Bachelor of Pharmacy in 1935 and the degree of Doctor of Philosophy and Doctor of Medicine in 1940, all from the University of Wisconsin. After interning at the Wisconsin General Hospital he held an American College of Physicians Fellowship in Medicine at Wayne University, 1941–43 and was, successively, instructor in medicine and assistant professor of physiology at Wayne University, 1943–45. Since 1945 he has been associate professor of physiology and medicine at the University of Oregon.

Doctor Ernest M. Brown, Jr. was named to receive the Ayerst, McKenna and Harrison Fellowship for 1948. He was born in 1919 and received the degree of Bachelor of Arts from West Virginia University in 1941 and of Doctor of Medicine from the University of Pennsylvania in 1944. He served as intern and junior resident at the University of Pennsylvania Hospital 1944–46. Since that time until April 1948 he has been a member of the Army Medical Corps. Doctor Brown will work at the George S. Cox Medical Research Institute with Dr. F. D. W. Lukens on lesions of the islands of Langerhans produced by intravascular infusion of glucose.

ANNOUNCEMENT OF THE AWARDS OF THE ASSOCIATION FOR 1949

Nominations for Awards

Three awards for meritorious work in endocrinology will be given at the next annual meeting of the Association. A special committee of five members of the Association chooses the recipients of these Awards, subject to ratification by the Council, and each member of the Association has the privilege of making one nomination for each award.

Nominations for the Awards should be made on special application forms which may be obtained from the Secretary, Dr. Henry H. Turner, 1200 North Walker Street, Oklahoma City 3, Oklahoma. All nominations, accompanied by a statement of the importance of the nominee's contribu-

tions to endocrinology and a bibliography of his most important papers with reprints if possible, should be sent to Dr. Turner's office not later than March 15, 1949.

THE E. R. SQUIBB AND SONS AWARD

The E. R. Squibb and Sons Award of $1,000.00 was established in 1939. It was given in 1940 to Dr. George W. Corner; in 1941 to Dr. Philip E. Smith; in 1942 to Dr. Fred C. Koch; in 1944 to Dr. Edward A. Doisy; in 1945 to Dr. E. C. Kendall; in 1946 to Dr. Carl G. Hartman; in 1947 to Drs. Carl F. and Gerty T. Cori and in 1948 to Dr. Fuller Albright. No award was made in 1943. No age or special limitation is stipulated by the donor of the award.

THE CIBA AWARD

The Ciba Award, established in 1942, is given in recognition of the meritorious accomplishment of an investigator, not over 35 years of age, in the field of clinical or pre-clinical endocrinology. In 1944 the Award was given to Dr. E. B. Astwood; in 1945 to Dr. Jane Anne Russell; in 1946 to Dr. Martin M. Hoffman; in 1947 to Dr. Choh Hao Li and in 1948 to Dr. Carl G. Heller. The Award is for $1,200.00. If within two years of the date of the Award, the recipient chooses to use it to aid in working in a laboratory other than the one in which he normally is located, the Award will be increased to $1,800.00.

THE AYERST, McKENNA & HARRISON FELLOWSHIP

The first Ayerst, McKenna & Harrison Fellowship was given to Dr. Samuel Dvoskin in 1947 and in 1948 it was given to Dr. Ernest M. Brown, Jr. This Fellowship is designed to assist men or women of exceptional promise in their progress toward a scientific career in endocrinology. The Fellowship may be awarded to an individual who possesses the Ph.D. or M.D. degree or to a candidate for either of these degrees. The stipend for the Fellowship will vary in accordance with the qualifications of the appointee, but will not exceed $2500.00. The Committee will, in reviewing the proposed program of study, consider the amount of time which the Fellow intends to spend in course work and/or teaching. The nominee must present evidence of scientific ability as attested by studies completed or in progress and/or the recommendation of responsible individuals, submit a program of proposed study, indicate one or more institutions where the proposed program shall be carried out and submit statements of approval from the investigators with whom he proposes to conduct his research.

THE 1949 MEETING OF THE ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS

The 31st Annual Meeting of the Association for the Study of Internal Secretions will be held at Haddon Hall, Atlantic City, New Jersey, June 3 and 4, 1949.

Inasmuch as the American Medical Association will be meeting in Atlantic City the following week, it is extremely important that hotel reservations be made at once directly with the hotel.

Further details concerning the meeting will be published at a later date.

ANNOUNCEMENT OF POST-GRADUATE COURSE IN ENDOCRINOLOGY

A postgraduate course in endocrinology will be given under the auspices of the American College of Physicians at the LaSalle Hotel in Chicago, November 1 to 6, 1948. The director of the course is Dr. Willard O. Thompson of Chicago.

Leading endocrinologists from all over the United States and Canada will take part in the teaching of this course. The fee for members of the College is $30.00 and for nonmembers, $60.00

Applications should be sent to Mr. E. R. Loveland, Executive Secretary American College of Physicians, Philadelphia 4, Pennsylvania.

PROGRAM OF THE 1948 LAURENTIAN HORMONE CONFERENCE

Forest Hills Hotel, Franconia, New Hampshire
September 13-18

Because of limited accommodations, attendance is by invitation. Correspondence should be addressed to: Dr. Gregory Pincus, Chairman, Committee on Arrangements, 222 Maple Avenue, Shrewsbury, Massachusetts.

I. STEROID HORMONE METABOLISM "IN VIVO" AND "IN VITRO"

Some aspects of Progesterone Metabolism
DR. G. F. MARRIAN, *University of Edinburgh*
Monday Evening, September 13

Recent Developments in Our Knowledge of Estrogen Metabolism
DR. R. D. H. HEARD and MRS. J. C. SAFFRAN, *McGill University*
Tuesday Morning, September 14

The Metabolism of Androgens by Tissues
DR. LEO T. SAMUELS, *University of Utah*
Tuesday Morning, September 14

The Metabolism of Estrogens with Particular Emphasis on Clinical Aspects of Physiology and Function of Ovarian Hormones
DR. ALBERT SEGALOFF, *Alton Ochsner Medical Foundation*
Tuesday Evening, September 14

II. THE ROLE OF HORMONES IN TISSUE AND BODY METABOLISM

The Antihormone Problem in Endocrine Therapy
DR. JAMES H. LEATHEM, *Rutgers University*
Wednesday Morning, September 15

Integration of the Metabolic Effects of Adrenal Cortical, Thyroid and Growth Hormones
DR. ABRAHAM WHITE, *University of California at Los Angeles*
Wednesday Morning, September 15

The Alterations in Metabolism Incident to Administration of Insulin, Adrenalin and Thyroid Substances, Studied with the Aid of Isotopes

DR. DEWITT STETTEN, JR., *Harvard University Medical School*

Wednesday Evening, September 15

The Pancreas as the Guardian of the Liver

DR. CHARLES H. BEST, *University of Toronto*

Thursday Morning September 16

Metabolic Changes in Man Following Adrenal and Pituitary Hormone Therapy

DR. GEORGE W. THORN, *Harvard University Medical School*

Thursday Morning, September 16

III. NEUROHUMORAL-HYPOTHALAMIC RELATIONSHIPS

Adrenal Function in Mental Disease

DR. GREGORY PINCUS, DR. HUDSON HOAGLAND, DR. HARRY FREEMAN and MR. FRED ELMADJIAN, *Worcester Foundation for Experimental Biology*

Thursday Evening, September 16

Manifestations of Altered Autonomic and Humoral Functions in Psychoneuroses

DR. ROBERT A. CLEGHORN, and DR. B. F. GRAHAM, *McGill University*

Friday Morning, September 17

Effects of Hypothalamic Lesions on Water and Energy Metabolism in the Rat

DR. JAMES A. F. STEVENSON, *Yale University*

Friday Morning, September 17

IV. THYROID PHYSIOLOGY AND FUNCTION

Physiologic Reactions of the Thyroid Stimulating Hormone

DR. RULON W. RAWSON and DR. WILLIAM L. MONEY, *Massachusetts General Hospital*

Friday Evening, September 17

The Metabolism of Iodine as Disclosed by the Use of Radioiodine (I131)

DR. F. R. KEATING, JR., and DR. ALEXANDER ALBERT, *The Mayo Clinic*

Saturday Morning, September 18

Radioiodine as a Diagnostic and Therapeutic Tool in Clinical Medicine

DR. S. M. SEIDLIN, *The Montefiore Hospital*

Saturday Morning, September 18